

Rec'd PATENT 24 JUN 2005

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
15 July 2004 (15.07.2004)

PCT

(10) International Publication Number
WO 2004/058750 A1

(51) International Patent Classification⁷: C07D 417/04,
417/14, 487/04, A61K 31/427, A61P 35/00 // (C07D
487/04, 253:00, 231:00)

(21) International Application Number:
PCT/GB2003/005651

(22) International Filing Date:
24 December 2003 (24.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0230162.0 24 December 2002 (24.12.2002) GB

(71) Applicant (for all designated States except US): METRIS
THERAPEUTICS LIMITED [GB/GB]; 400 Thames
Valley Park Drive, Reading RG6 1PT (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): KNOX, Peter

[GB/GB]; 400 Thames Valley Park Drive, Reading
RG6 1PT (GB). O'SULLIVAN, Michele [GB/GB]; 400
Thames Valley Park Drive, Reading RG6 1PT (GB).
LENTFER, Heike [GB/GB]; 400 Thames Valley Park
Drive, Reading RG6 1PT (GB).

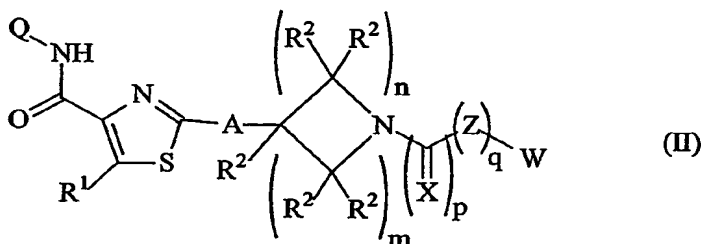
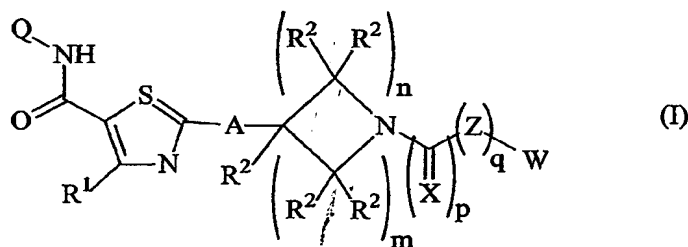
(74) Agents: GOODFELLOW, Hugh, Robin et al.; Carp-
maels & Ransford, 43-45 Bloomsbury Square, London
WC1A 2RA (GB).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR,
CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,
KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN,
MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU,
SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,
UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (BW, GH,
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,

[Continued on next page]

(54) Title: PIPERIDINYL-THIAZOLE CARBOXYLIC ACID DERIVATIVES AS ANGIOGENESIS INHIBITORS



(57) Abstract: This invention relates to compounds of formula (I) and (II) that are useful in treating vascular endothelial growth factor (VEGF)-mediated disorders, particularly endometriosis and acute macular degenerative disorder. The invention also relates to a topical system for the treatment of acute macular degenerative disorder comprising a VEGF inhibitor.

WO 2004/058750 A1

WO 2004/058750 A1



SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Published:

— *with international search report*

PIPERIDINYL-THIAZOLE CARBOXYLIC ACID DERIVATIVES AS ANGIOGENESIS INHIBITORS

Technical Field

- 5 This invention relates to compounds that are useful in treating vascular endothelial growth factor (VEGF)-mediated disorders. In particular, this invention relates to compounds useful in treating endometriosis. The invention also relates to the use of these compounds and to pharmaceutical compositions comprising these compounds.

10 Technical Background

- Vasculogenesis and angiogenesis play important roles in a variety of physiological processes such as embryonic development, wound healing, organ regeneration and female reproductive processes. Unregulated angiogenesis occurs in a number of disease states.
- 15 These include benign conditions such as endometriosis but also life-threatening conditions such as malignant tumours. The diverse disease states in which unregulated angiogenesis is present have been grouped together as angiogenic dependent or angiogenic associated diseases (Klagsburn & Soker, 1993, Current Biology 3(10):699-702; Folkman, 1991, J. Natl., Cancer Inst. 82:4-6; Weidner, et al., 1991, New Engl. J. Med. 324:1-5. Folkman &
- 20 Shing, 1992, J. Biological Chem. 267(16):10931-34).

- Several polypeptides with in vitro endothelial cell growth promoting activity have been identified but VEGF has been reported to be an endothelial cell specific mitogen (Ferrara & Henzel, 1989, Biochem. Biophys. Res. Comm. 161:851-858; Vaisman et al., 1990, J.
- 25 Biol. Chem. 265:19461-19566).

- VEGF is a family of dimeric glycoproteins that belong to the platelet derived growth factor (PDGF) superfamily of growth factors. In addition to VEGF-A, VEGF-B, VEGF-C and VEGF-D there is the so-called placental growth factor (PlGF). Some of the genes for
- 30 these growth factors can be expressed as different isoforms. For example the VEGF-A gene is differentially spliced into a number of isoforms the most common messenger RNA's encoding polypeptides of 121, 165 and 189 amino acids. The compounds

described in this invention are likely to have inhibitory activity against the VEGF family and possibly against other related families to a greater or lesser extent.

Thus the ability to inhibit the activity of VEGF and its stimulation of new blood vessel
5 formation represents a selective pharmaceutical approach for a number of clinical conditions.

As mentioned above, one disease in which VEGF plays a role is endometriosis. Endometriosis is the name given to the disease resulting from the presence of endometrial
10 cells outside of the uterine cavity. This disease affects women during their childbearing years with deleterious social, sexual and reproductive consequences. Endometriosis has been proposed as one of the most commonly-encountered diseases of gynaecology, with the incidence of endometriosis in the general population being estimated to be around 5%, although it is thought that at least 25% of women in their thirties and forties may have
15 endometrial lesions from this disease.

The development and maintenance of endometriosis involves the establishment and subsequent sustained growth of endometrial cells at ectopic sites, most commonly the pelvic peritoneum and ovaries, following retrograde menstruation (see Thomas & Prentice
20 (1992) *Repro. Med. Rev.* (1): 21-36). Implantation of autologous non-malignant ectopic tissue is a unique phenomenon suggesting that an abnormal host response may be present in women who develop this disease. This theory is supported by the fact that only a minority of women will develop the disease in spite of the common occurrence of retrograde menstruation as a source of endometrial tissue.

25

There are many theories proposed for the origin of endometriosis and various cellular and biochemical constituents of the peritoneal fluid have been reported to play an important role in the pathogenesis of this disease. Alterations in multiple aspects of both humoral immunity and cell-mediated immunity have also been reported in suffering individuals.

30

The heritable aspects of endometriosis have been investigated in several studies (Moen & Magnus (1993) *Acta Obstet. Gynecol. Scand.*, 72: 560-564; Kennedy *et al.*, (1995) *J.*

Assist. Repro. Gen., 12(1): 32-35; Malinak *et al* (1986) Am. J. Obstet. Gynecol., 137(3): 332-337; Treloar *et al.*, (1999) Fertility Sterility 71(4) 701-710). On the basis of these studies, it has been hypothesised that endometriosis has in part a genetic basis. However, the precise aetiology of this disease still remains unknown.

5

The growth and development of endometrial tissue appears to depend on the presence of oestrogen. Drugs have thus been developed that reduce the body's oestrogen content in order to reduce the growth of endometrial implants at ectopic sites. Strategies include mimicking pregnancy, preventing ovulation using contraceptive agents, blocking the action
10 of progesterone and mimicking the menopause. Although some of these drugs have proved successful, many cause unpleasant side-effects including post-menopausal like side effects and infertility, which mean that treatment must be discontinued to avoid the side-effects becoming permanent. Furthermore, all drugs described to date act by relieving the symptoms of the disease and are not in any sense curative. This makes a patient
15 permanently dependent on the drug if the symptoms of disease are to be kept at bay.

Presently, the only treatment of endometriosis that is effective in the long term involves surgery. Therefore, there remains a great need for the discovery of agents with effective prophylactic, therapeutic and diagnostic value against endometriosis.

20

VEGF, also known as vascular permeability factor is secreted by tumours (Dvorak, H. *et al.*, (1979) J. Immunol., 122, 166-174; it is a multi-functional cytokine that promotes the formation of blood vessels (angiogenesis). The growth of most tumours is dependent on the development of an adequate blood supply and therefore the prevention of angiogenesis
25 by the inhibition of VEGF provides a potential strategy for the development of anti-cancer pharmaceuticals.

The expression of VEGF correlates with poor prognosis (Tabone, M. D. *et al.*, (2001) Clin. Cancer Res., 7, 538-543) and has been detected in renal cell carcinoma (Slaton, J. W. *et al.*,
30 (2001) Am. J. Path., 158, 735-743), mammary carcinoma (Adams, J. *et al.*, (2000) Cancer Res., 60, 2898-2905), head and neck squamous cell carcinoma (Minet, H. *et al.*, (2000) Br. J. Cancer, 83, 775-781), bladder cancer (Inoue, K. *et al.*, (2000) Clin. Cancer Res., 6, 4866-

4873), oesophageal carcinoma (Shih, C. H. et al., (2000) Clin. Cancer Res., 6, 1161-1168), osteosarcoma (Kaya, M. et al., (2000) Clin. Cancer Res., 6, 572-577), colonic carcinoma (Cascinu, S. et al., (2000) Clin. Cancer Res., 6, 2803-2807), ovarian carcinoma (Shen, G. H. et al., (2000) Br. J. Cancer, 83, 196-203), carcinoma of the cervix (Loncaster, J. A. et al., (2000) Br. J. Cancer, 83, 620-625), soft tissue sarcomas (Yudoh, K. et al., (2001) Br. J. Cancer, 84, 1610-1615), astrocytoma (Abdulrauf, S. I. et al., (1998) J. Neurosurg., 88, 513-520) and prostate carcinoma (Borre, M. et al., (2000) Clin. Cancer Res., 6, 1882-1890). Inhibition of VEGF and thereby reducing the ability of the tumour to become vascularized, either alone or in combination with other treatments such as chemotherapy or radiotherapy may therefore have clinical utility in these and other human and animal tumours.

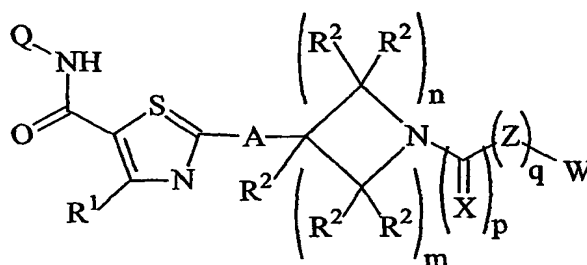
A number of non-oncological clinical indications involve abnormally increased angiogenesis and the inventions described herein may be the basis for therapeutic intervention. Macular degeneration and retinopathy can occur as a result of the ageing process or occur as a result of other diseases in particular diabetes. High levels of VEGF have been implicated in these conditions (Funatsu, H. et al., (2002) J. Cataract Refract. Surg. 28, 1355; Noma, H. et al., (2002) Arch. Ophthalmol. 120, 1075-80). It has been suggested that inhibition of VEGF may be useful (Aiello, L.P. (1997) Ophthalmic Res., 29, 354-62) and in particular may prevent the oedema that occurs at the early stages of diabetic retinopathy (Lu, M. et al., (2002) Ophthalmol. Clin. North Am., 15, 69-79). Diabetic nephropathy and neuropathy may have a common biochemical dysfunction to retinopathy (Tilton, R.G. (2002) Microsc. Res. Tech., 57, 390-407) and an anti-VEGF pharmaceutical approach may be appropriate.

Inhibition of VEGF may also be a suitable therapeutic strategy in atheroma (Blann, A.D., (2002) Clin. Sci. 102, 187-94) and in rheumatoid arthritis (Afuwape, A.O., (2002) Histol. Histopathol., 17, 961-72) and psoriasis (Creamer, D. et al., (2002) Arch. Dermatol., 138, 791-6); VEGF has been implicated in the pathogenesis of both conditions.

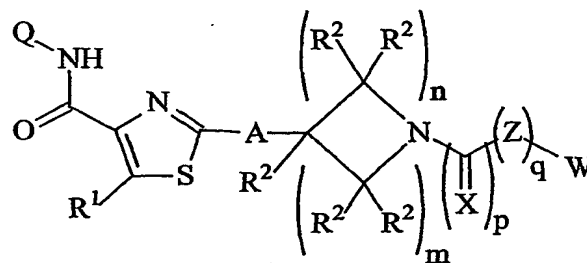
It is an object of the present invention to provide compounds that are useful in treating VEGF-related disorders.

Summary of the Invention

According to a first embodiment of the present invention there is provided a compound of
 5 formula (I) or formula (II):



(I)



(II)

wherein:

Q is an optionally substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, alkylthio, aralkylthio, amino, alkylamino, dialkylamino, carboxyl, carboxylalkyl,
 15 esterified carboxyl, alkylsulfoxyl, alkylsulfonyl, nitro, carbonitrile, carbo-alkoxy, carbo-aryloxy, or heterocyclic group;

A is a single bond or alkylene;

X is O or S;

Z is O, S or NR³;

20 p is 0 or 1

q is 0 or 1;

n is an integer from 0 to 10;

m is an integer from 0 to 10;

W is an optionally substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, alkylthio, aralkylthio, amino, alkylamino, dialkylamino, carboxyl, carboxylalkyl, esterified carboxyl, alkylsulfoxyl, alkylsulfonyl, nitro, carbonitrile, carbo-alkoxy, carbo-aryloxy, or heterocyclic group;

5 R¹ is H or alkyl;

R² is independently H or alkyl; and

R³ is H or alkyl;

or a pharmaceutically acceptable derivative thereof.

10 The term "pharmaceutically acceptable derivative" as used herein, means any pharmaceutically acceptable salt, addition compound, or any other compound which upon administration to a recipient is capable of providing, whether directly or indirectly, a compound of the invention or a pharmaceutically acceptable metabolite.

15 The term "pharmaceutically acceptable metabolite" as used herein, means a metabolite or residue of a compound of the invention which gives rise to a biological activity exhibited by the compounds of the invention.

The term "pharmaceutically acceptable salt", as used herein, refers to a salt prepared from
20 pharmaceutically acceptable non-toxic acids or bases including inorganic or organic acids and bases.

Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, sulfuric, and phosphoric acids. Appropriate organic acids may be selected, for example, from aliphatic,
25 aromatic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, glucuronic, maleic, furoic, glutamic, benzoic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, benzenesulfonic, stearic, sulfanilic, algenic, and galacturonic. Examples of such inorganic bases include metallic salts made from aluminium, calcium,
30 lithium, magnesium, potassium, sodium, and zinc. Appropriate organic bases may be selected, for example, from N,N-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumaine (N-methylglucamine), and procaine.

As used herein, the term "alkyl" means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic, the alkyl group is preferably C₃ to C₁₂, more preferably C₅ to C₁₀, more preferably C₅, C₆ or C₇. Where acyclic, the alkyl group is preferably C₁ to C₁₀, more preferably C₁ to C₆, more preferably methyl, ethyl, propyl (n-propyl or isopropyl), butyl (n-butyl, isobutyl or tertiary-butyl) or pentyl (including n-pentyl and iso-pentyl), more preferably methyl. It will be appreciated therefore that the term "alkyl" as used herein includes alkyl (branched or unbranched), alkenyl (branched or unbranched), alkynyl (branched or unbranched), cycloalkyl, cycloalkenyl and cycloalkynyl.

Saturated hydrocarbyl radicals are generally preferred.

As used herein, the term "lower alkyl" means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical, wherein a cyclic lower alkyl group is C₅, C₆ or C₇, and wherein an acyclic lower alkyl group is C₁ to C₆, that is, methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl or tertiary-butyl), more preferably methyl.

An alkyl group may be substituted or unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 or 2 substituents. Substituents may include halogen atoms and halomethyl groups such as CF₃ and CCl₃; oxygen containing groups such as oxo, hydroxy, carboxy, carboxyalkyl, alkoxy, alkoyl, alkoyloxy, aryloxy, aryloyl and aryloyloxy; nitrogen containing groups such as amino, amido, alkylamino, dialkylamino, cyano, azide, nitrato and nitro; sulphur containing groups such as thiol, alkylthiol, sulphonyl and sulphoxide; heterocyclic groups containing one or more, heteroatom, such as thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolynyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl, carbolinyl, oxadiazolyl, thiadiazolyl,

triazolyl, tetrazolyl and pyrimidinyl; alkyl groups, which may themselves be substituted; and aryl groups, which may themselves be substituted, such as phenyl and substituted phenyl.

As used herein, the term "alkylene" means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenylene or alkynylene) hydrocarbylene radical. Where cyclic, the alkylene group is preferably C₃ to C₁₂, more preferably C₅ to C₁₀, more preferably C₅ to C₇. Where acyclic, the alkylene group is preferably C₁ to C₁₆, more preferably C₁ to C₄, more preferably methylene.

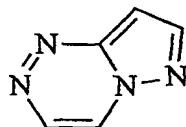
10 An alkylene group may be substituted or unsubstituted, preferably unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 substituent. Substituents may include halogen atoms and halomethyl groups such as CF₃ and CCl₃; oxygen containing groups such as oxo, hydroxy, carboxy, carboxyalkyl, alkoxy, alkoyl, alkoyloxy, aryloxy, aryloyl and aryloyloxy; nitrogen containing groups such as amino, amido, alkylamino, dialkylamino, cyano, azide, nitrato and nitro; sulphur containing groups such as thiol, alkylthiol, sulphonyl and sulphoxide; heterocyclic groups containing one or more, preferably one, heteroatom, such as thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazoliny, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl and carbolinyl; alkyl groups, which may themselves be substituted; and aryl groups, which may themselves be substituted, such as phenyl and substituted phenyl.

As used herein, the term "aryl" means a cyclic or bicyclic aromatic group, such as phenyl or naphthyl. C₆₋₁₂ (e.g. C₆₋₁₀) aryl groups are preferred. An aryl group may be substituted or unsubstituted, preferably unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 substituent. Substituents may include halogen atoms and halomethyl groups such as CF₃ and CCl₃; oxygen containing groups such as oxo, hydroxy, carboxy, carboxyalkyl, alkoxy, alkoyl, alkoyloxy, aryloxy, aryloyl and aryloyloxy;

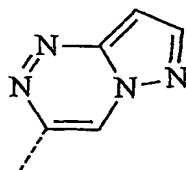
nitrogen containing groups such as amino, amido, alkylamino, dialkylamino, cyano, azide, nitrate and nitro; sulphur containing groups such as thiol, alkylthiol, sulphonyl and sulfoxide; heterocyclic groups containing one or more, preferably one, heteroatom, such as thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, 5 pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranal, pyronyl, pyridyl, pyrazinyl, pyridazinyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolyl, 7-azaindolyl, isoindazolyl, benzopyranal, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl and carbolinyl; alkyl groups, which may 10 themselves be substituted; and aryl groups, which may themselves be substituted, such as phenyl and substituted phenyl.

As used herein, the term "heterocyclic" means a saturated or unsaturated cyclic or bicyclic group containing one or more heteroatoms, such as thienyl, furanyl, pyrrolyl, imidazolyl, 15 pyrazolyl, thiazolyl, oxazolyl, isoxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranal, pyronyl, pyridyl, pyrazinyl, pyridazinyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolyl, 7-azaindolyl, isoindazolyl, benzopyranal, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolyl, quinazolinyl, pyridopyridyl, benzoxazinyl, 20 quinoxadinyl, chromenyl, chromanyl, isochromanyl, carbolinyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl and pyrimidinyl.

The term "heterocyclic group" also includes groups derived from:



25 preferably



Heterocyclic groups containing from 5 to 12 (e.g. 5 to 10) atoms are preferred. Heterocyclic groups preferably contain 1, 2, 3 or 4 heteroatoms. Preferred heteroatoms are N, O and S.

- 5 A heterocyclic group may be substituted or unsubstituted, preferably unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 substituent. Substituents may include halogen atoms and halomethyl groups such as CF₃ and CCl₃; oxygen containing groups such as oxo, hydroxy, carboxy, carboxyalkyl, alkoxy, alkoxy, alkoyl, alkoyloxy, aryloxy, aryloyl and aryloyloxy; nitrogen containing groups such as amino, amido, alkylamino, dialkylamino, cyano, azide, nitrate and nitro; sulphur containing groups such as thiol, alkylthiol, sulphonyl and sulfoxide; heterocyclic groups containing one or more, preferably one, heteroatom, such as thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranal, pyronal, pyridyl, pyrazinyl, pyridazinyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranal, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl and carbolinyl; alkyl groups, which may themselves be substituted; and aryl groups, which may themselves be substituted, such as phenyl and substituted phenyl.

When a heterocyclic group, which is itself a substituent, is substituted, it is preferably substituted with lower alkyl, more preferably methyl.

- 25 As used herein, the term "aralkyl" means aryl-alkyl- (e.g. benzyl).

As used herein, the term "alkoxy" means alkyl-O-. As used herein, the term "lower alkoxy" means loweralkyl-O-. As used herein, the term "aryloxy" means aryl-O-. As used herein, the term "aralkoxy" means aralkyl-O-,

As used herein, substituents which are nitrogen containing groups include $-C(O)-NH_2$, $-C(O)-NHR^4$ and $-C(O)-NR^4_2$, where R^4 is independently an optionally substituted alkyl or aryl (preferably alkyl).

- 5 As used herein, substituents which are sulphur containing groups include $-S(O)_2-H$, $-S(O)_2-R^4$, $-S(O)-H$ and $-S(O)-R^4$, where R^4 is an optionally substituted alkyl or aryl (preferably alkyl).

- As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical,
10 preferably a fluorine or chlorine radical.

Compounds of the invention of formula (II) are preferred.

Preferably, A is a single bond.

15

Preferably, X is O. Alternatively, it is preferred that X is S and Z is N.

Preferably, X is O. Alternatively, it is preferred that X is S and Z is NR^3 .

- 20 Preferably, R^3 is H.

Preferably, $p = 1$.

Preferably, $q = 0$.

25

Preferably, the sum $n + m$ is an integer from 2 to 10, more preferably 2 to 6, more preferably 2 to 4, more preferably 3 or 4, most preferably 4.

Preferably, n is from 0 to 3, preferably 2.

30

Preferably, m is from 0 to 3, preferably 2.

Preferably, $n = 2$ and $m = 2$.

Preferably, R^1 is H.

5 Preferably, each R^2 is H.

The substituents Q and W may be substituted or unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 or 2 substituents. Substituents may include halogen atoms and halomethyl groups such as CF_3 and CCl_3 ; oxygen containing
10 groups such as oxo, hydroxy, carboxy, carboxyalkyl, alkoxy, alkoxymethyl, alkyl, alkoxyloxy, aryloxy, aryloxy and aryloxyloxy; nitrogen containing groups such as amino, amido, alkylamino, dialkylamino, cyano, azide, nitrate and nitro; sulphur containing groups such as thiol, alkylthiol, sulphonyl and sulfoxide; heterocyclic groups containing one or more, heteroatom, such as thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl,
15 oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolyl, pyrazolidinyl, tetrahydrofuranyl, pyranal, pyranal, pyridyl, pyrazinyl, pyridazinyl, benzofuranyl, isobenzofuranyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolyl, 7-azaindolyl, isoindazolyl, benzopyranal, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl,
20 isochromanyl, carbolinyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl and pyrimidinyl; alkyl groups, which may themselves be substituted; and aryl groups, which may themselves be substituted, such as phenyl and substituted phenyl.

Preferably, Q is an optionally substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, carboxyl,
25 carboxylalkyl, esterified carboxyl, alkylsulfonyl or heterocyclic group.

More preferably, Q comprises an optionally substituted aryl or heterocyclic group. Still more preferably, Q is an optionally substituted aryl or heterocyclic group. A preferred aryl group is phenyl. A preferred heterocyclic group is an unsaturated heterocyclic group, more
30 preferably a monocyclic unsaturated heterocyclic group.

When substituted, Q is preferably independently substituted by one or more (e.g. 1, 2 or 3) of: halogen; trihalomethyl; $-\text{NO}_2$; $-\text{CN}$; $-\text{Y}-\text{C}(=\text{Y})-\text{R}^5$; $-\text{C}(=\text{Y})-\text{R}^5$; $-\text{C}(=\text{Y})-\text{Y}-\text{R}^5$; $-\text{Y}-\text{C}(=\text{Y})-\text{Y}-\text{R}^5$; $-\text{SOR}^5$; $-\text{S}(=\text{O})_2\text{R}^5$; $-\text{Y}-\text{S}(=\text{O})\text{OR}^5$; $-\text{Y}-\text{S}(=\text{O})_2\text{R}^5$; $-\text{S}(=\text{O})_2-\text{YR}^5$; $-\text{Y}-\text{S}(=\text{O})_2-\text{YR}^5$; $-\text{R}^5$; $-\text{YR}^5$; or alkyl (preferably methyl) substituted with one or more (e.g. 1, 2 or 3, preferably 1) of halogen, trihalomethyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{Y}-\text{C}(=\text{Y})-\text{R}^5$, $-\text{C}(=\text{Y})-\text{R}^5$, $-\text{C}(=\text{Y})-\text{Y}-\text{R}^5$, $-\text{Y}-\text{C}(=\text{Y})-\text{Y}-\text{R}^5$, $-\text{SOR}^5$, $-\text{S}(=\text{O})_2\text{R}^5$, $-\text{Y}-\text{S}(=\text{O})\text{OR}^5$, $-\text{Y}-\text{S}(=\text{O})_2\text{R}^5$, $-\text{S}(=\text{O})_2-\text{YR}^5$, $-\text{Y}-\text{S}(=\text{O})_2-\text{YR}^5$ or $-\text{YR}^5$. Y is independently O, S or NR^5 , and R^5 is independently H or an optionally substituted alkyl, aryl or heterocyclic group (preferably H or alkyl). More preferred substituents are: halogen; trihalomethyl; $-\text{NO}_2$; $-\text{CN}$; $-\text{CO}_2\text{H}$; $-\text{CO}_2\text{R}^5$; $-\text{C}(=\text{O})\text{H}$; $-\text{C}(=\text{O})\text{R}^5$; $-\text{OC}(=\text{O})\text{R}^5$; $-\text{OC}(=\text{O})\text{OR}^5$; $-\text{C}(=\text{O})\text{NH}_2$; $-\text{C}(=\text{O})\text{NR}^5_2$; $-\text{N}(\text{R}^5)\text{C}(=\text{O})\text{R}^5$; $-\text{N}(\text{R}^5)\text{C}(=\text{O})\text{OR}^5$; $-\text{OC}(=\text{O})\text{NR}^5_2$; $-\text{N}(\text{R}^5)\text{C}(=\text{O})\text{NR}^5_2$; $-\text{C}(=\text{S})\text{NH}_2$; $-\text{C}(=\text{S})\text{NR}^5_2$; $-\text{N}(\text{R}^5)\text{C}(=\text{S})\text{R}^5$; $-\text{N}(\text{R}^5)\text{C}(=\text{S})\text{NR}^5_2$; $-\text{C}(=\text{NH})\text{NH}_2$; $-\text{C}(=\text{NR}^5)\text{NR}^5_2$; $-\text{N}(\text{R}^5)\text{C}(=\text{NR}^5)\text{R}^5$; $-\text{N}(\text{R}^5)\text{C}(=\text{NR}^5)\text{NR}^5_2$; $-\text{SOR}^5$; $-\text{S}(=\text{O})_2\text{R}^5$; $-\text{S}(=\text{O})_2\text{OH}$; $-\text{S}(=\text{O})_2\text{OR}^5$; $-\text{S}(=\text{O})_2\text{NR}^5_2$; $-\text{N}(\text{R}^5)\text{SO}_2\text{R}^5$; $-\text{N}(\text{R}^5)\text{SO}_2\text{NR}^5_2$; $-\text{NR}^5_2$; $-\text{R}^5$; $-\text{YR}^5$; or alkyl (preferably methyl) substituted with one or more (e.g. 1, 2 or 3, preferably 1) of halogen, trihalomethyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{R}^5$, $-\text{C}(=\text{O})\text{H}$, $-\text{C}(=\text{O})\text{R}^5$, $-\text{OC}(=\text{O})\text{R}^5$, $-\text{OC}(=\text{O})\text{OR}^5$, $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{NR}^5_2$, $-\text{N}(\text{R}^5)\text{C}(=\text{O})\text{R}^5$, $-\text{N}(\text{R}^5)\text{C}(=\text{O})\text{OR}^5$, $-\text{OC}(=\text{O})\text{NR}^5_2$, $-\text{N}(\text{R}^5)\text{C}(=\text{O})\text{NR}^5_2$, $-\text{C}(=\text{S})\text{NH}_2$, $-\text{C}(=\text{S})\text{NR}^5_2$, $-\text{N}(\text{R}^5)\text{C}(=\text{S})\text{R}^5$, $-\text{N}(\text{R}^5)\text{C}(=\text{S})\text{NR}^5_2$, $-\text{C}(=\text{NH})\text{NH}_2$, $-\text{C}(=\text{NR}^5)\text{NR}^5_2$, $-\text{N}(\text{R}^5)\text{C}(=\text{NR}^5)\text{R}^5$, $-\text{N}(\text{R}^5)\text{C}(=\text{NR}^5)\text{NR}^5_2$, $-\text{SOR}^5$, $-\text{S}(=\text{O})_2\text{R}^5$, $-\text{S}(=\text{O})_2\text{OH}$, $-\text{S}(=\text{O})_2\text{OR}^5$, $-\text{S}(=\text{O})_2\text{NR}^5_2$, $-\text{N}(\text{R}^5)\text{SO}_2\text{R}^5$, $-\text{N}(\text{R}^5)\text{SO}_2\text{NR}^5_2$, $-\text{NR}^5_2$ or $-\text{YR}^5$. Still more preferred substituents are: halogen; $-\text{CN}$; $-\text{CO}_2\text{H}$; $-\text{CO}_2\text{R}^5$; $-\text{C}(=\text{O})\text{R}^5$; $-\text{C}(=\text{O})\text{NH}_2$; $-\text{C}(=\text{O})\text{NR}^5_2$; $-\text{N}(\text{R}^5)\text{C}(=\text{O})\text{R}^5$; $-\text{C}(=\text{S})\text{NH}_2$; $-\text{C}(=\text{S})\text{NR}^5_2$; $-\text{C}(=\text{NH})\text{NH}_2$; $-\text{C}(=\text{NR}^5)\text{NR}^5_2$; $-\text{S}(=\text{O})_2\text{R}^5$; $-\text{NR}^5_2$; $-\text{R}^5$; $-\text{YR}^5$ or alkyl (preferably methyl) substituted with $-\text{C}(=\text{O})\text{NR}^5_2$. Still more preferred substituents are $-\text{Cl}$, $-\text{OMe}$, $-\text{C}(=\text{O})\text{NH}_2$ and $-\text{CH}_2-\text{C}(=\text{O})\text{NH}_2$.

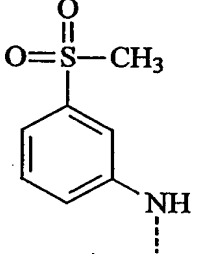
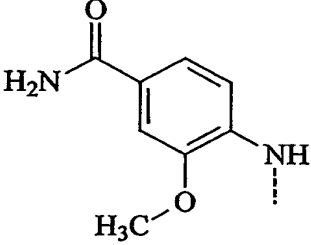
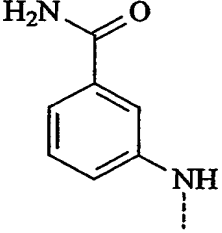
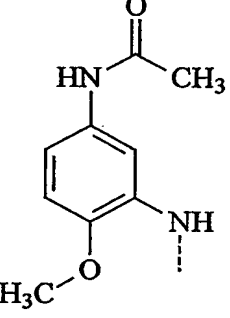
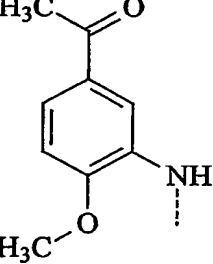
When Q is substituted by $-\text{R}^5$, it is preferred that R^5 is an optionally substituted heterocyclic group, preferably an unsaturated heterocyclic group, preferably a monocyclic unsaturated heterocyclic group (e.g. oxazolyl, tetrazolyl or oxazolyl substituted with lower alkyl, e.g. methyl).

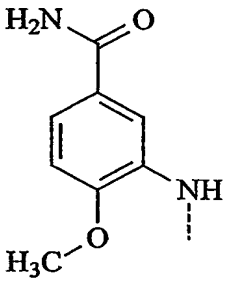
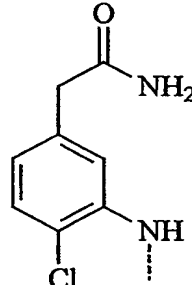
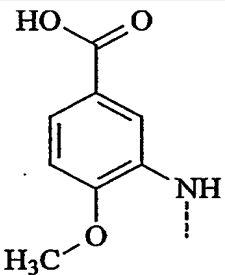
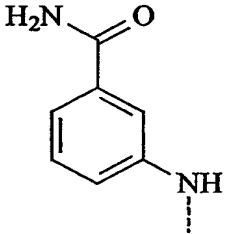
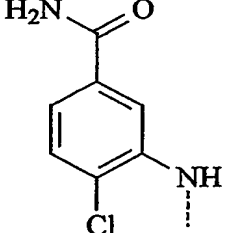
Preferably Q is a heterocyclic group, optionally substituted with 1, 2 or 3 substituents, preferably 2 substituents. When Q is a heterocyclic group, it is preferably thienyl (e.g. 2-thienyl) or furanyl (e.g. 2-furanyl).

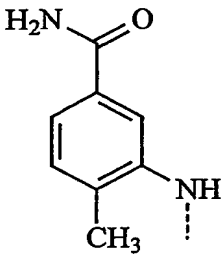
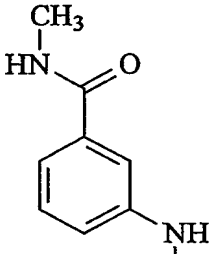
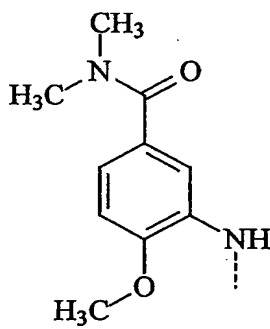
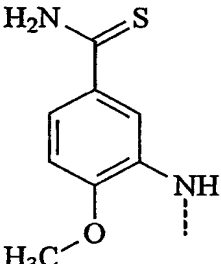
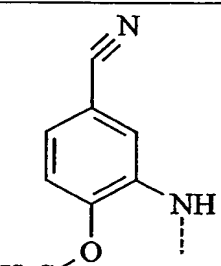
- 5 Preferably, Q is a phenyl group optionally substituted with 1, 2 or 3 substituents, preferably 2 substituents. Preferably Q is a phenyl group having at least one substituent selected from alkoxy, amide, carboxy, carboxylalkyl, alkoxy, cyano, halogen and a heterocyclic group.
- 10 Preferably Q is a phenyl group substituted with at least one group selected from methoxy, cyano, chlorine, fluorine, oxazolyl, tetrazolyl, oxazolyl substituted with lower alkyl, -C(O)NH₂, -C(O)NHR, -C(O)NR₂, -C(S)NH₂ and -NHC(O)R, where R is lower alkyl, preferably methyl.
- 15 Q may be thiophenyl. Preferably, Q is thiophenyl substituted with a methoxy, cyano, chlorine, -C(O)NH₂, -C(O)NHR, -C(O)NR₂, -C(S)NH₂ or -NHC(O)R group, where R is lower alkyl, preferably methyl.
- 20 Q may be furanyl. Preferably, Q is furanyl substituted with a methoxy, cyano, chlorine, -C(O)NH₂, -C(O)NHR, -C(O)NR₂, -C(S)NH₂ or -NHC(O)R group, where R is lower alkyl, preferably methyl.
- 25 Q may be thienyl. Preferably, Q is thienyl optionally substituted with a methoxy, cyano, chlorine, -C(O)NH₂, -C(O)NHR, -C(O)NR₂, -C(S)NH₂ or -NHC(O)R group, where R is lower alkyl, preferably methyl.

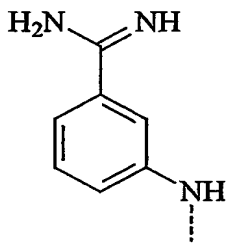
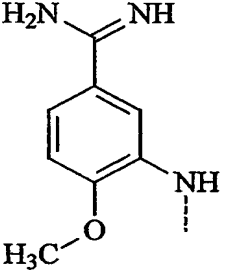
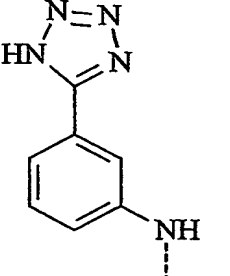
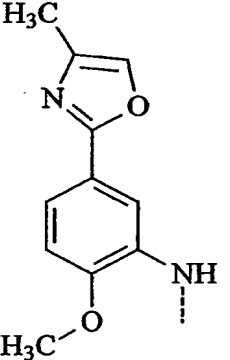
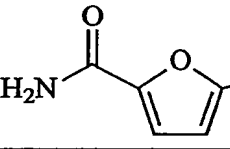
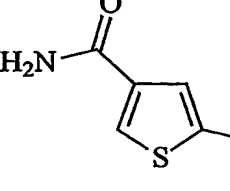
Preferably Q is a radical selected from the radicals set out in Table 1. It will be understood that the linking nitrogen atom shown (-NH--) does not form part of the radical Q.

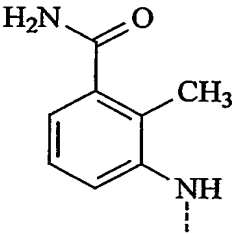
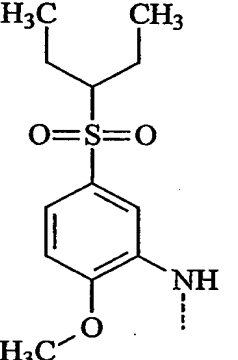
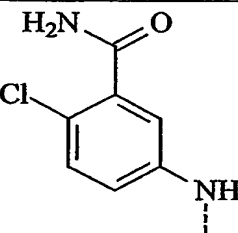
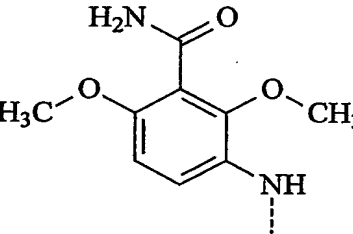
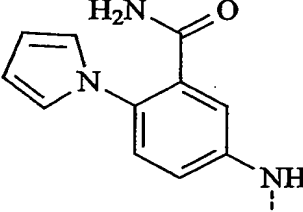
Table 1

Q	Radical
Q ¹	 <chem>CS(=O)(=O)c1ccc(N)cc1</chem>
Q ²	 <chem>CC(=O)Nc1ccc(N)cc1OC</chem>
Q ³	 <chem>CC(=O)Nc1ccc(N)cc1</chem>
Q ⁴	 <chem>CC(=O)Nc1ccc(N)cc1OC</chem>
Q ⁵	 <chem>CC(=O)c1ccc(N)cc1OC</chem>

Q ⁶	 <p>Chemical structure of 3-amino-4-methoxybenzamide: A benzene ring with an amide group (-CONH₂) at position 1, a methoxy group (-OCH₃) at position 4, and an amino group (-NH₂) at position 3. The amino group is shown with a dashed bond to the ring.</p>
Q ⁷	 <p>Chemical structure of 3-amino-4-chlorobenzamide: A benzene ring with an amide group (-CONH₂) at position 1, a chlorine atom (-Cl) at position 4, and an amino group (-NH₂) at position 3. The amino group is shown with a dashed bond to the ring.</p>
Q ⁸	 <p>Chemical structure of 3-amino-4-methoxybenzoic acid: A benzene ring with a carboxylic acid group (-COOH) at position 1, a methoxy group (-OCH₃) at position 4, and an amino group (-NH₂) at position 3. The amino group is shown with a dashed bond to the ring.</p>
Q ⁹	 <p>Chemical structure of 3-aminoaniline: A benzene ring with an amine group (-NH₂) at position 1 and an amino group (-NH₂) at position 3. The amino group at position 3 is shown with a dashed bond to the ring.</p>
Q ¹⁰	 <p>Chemical structure of 3-amino-4-chloroaniline: A benzene ring with an amine group (-NH₂) at position 1, a chlorine atom (-Cl) at position 4, and an amino group (-NH₂) at position 3. The amino group at position 3 is shown with a dashed bond to the ring.</p>

Q ¹¹	 <p>Chemical structure of 3-amino-4-methylbenzamide: A benzene ring with an amide group (-C(=O)NH₂) at position 1, an amino group (-NH₂) at position 3, and a methyl group (-CH₃) at position 4. A dashed line is shown below the amino group.</p>
Q ¹²	 <p>Chemical structure of N-methyl-3-aminobenzamide: A benzene ring with an amide group (-C(=O)NHCH₃) at position 1, an amino group (-NH₂) at position 3, and a dashed line below the amino group.</p>
Q ¹³	 <p>Chemical structure of N-methyl-3-amino-4-methoxybenzamide: A benzene ring with an amide group (-C(=O)N(CH₃)CH₃) at position 1, an amino group (-NH₂) at position 3, a methoxy group (-OCH₃) at position 4, and a dashed line below the amino group.</p>
Q ¹⁴	 <p>Chemical structure of N-methyl-3-amino-4-methoxybenzothioamide: A benzene ring with a thioamide group (-C(=S)NH₂) at position 1, an amino group (-NH₂) at position 3, a methoxy group (-OCH₃) at position 4, and a dashed line below the amino group.</p>
Q ¹⁵	 <p>Chemical structure of N-methyl-3-amino-4-methoxybenzonitrile: A benzene ring with a nitrile group (-C≡N) at position 1, an amino group (-NH₂) at position 3, a methoxy group (-OCH₃) at position 4, and a dashed line below the amino group.</p>

Q ¹⁶	 <p>Chemical structure of 3-amino-NH-phenylhydrazide. It consists of a benzene ring with a hydrazide group (-C(=O)NHNH₂) at the 1-position and an amino group (-NH₂) at the 3-position. The amino group is attached to a dashed line.</p>
Q ¹⁷	 <p>Chemical structure of 3-amino-4-methoxy-NH-phenylhydrazide. It consists of a benzene ring with a hydrazide group (-C(=O)NHNH₂) at the 1-position, a methoxy group (-OCH₃) at the 4-position, and an amino group (-NH₂) at the 3-position. The amino group is attached to a dashed line.</p>
Q ¹⁸	 <p>Chemical structure of 3-amino-NH-phenylhydrazide with a diazo group. It consists of a benzene ring with a diazo group (-N=N-NH-) at the 1-position and an amino group (-NH₂) at the 3-position. The amino group is attached to a dashed line.</p>
Q ¹⁹	 <p>Chemical structure of 3-amino-4-methoxy-NH-phenylhydrazide with a furan ring. It consists of a benzene ring with a furan ring at the 1-position, a methoxy group (-OCH₃) at the 4-position, and an amino group (-NH₂) at the 3-position. The amino group is attached to a dashed line.</p>
Q ²⁰	 <p>Chemical structure of 3-amino-4-methoxy-NH-phenylhydrazide with a furan ring. It consists of a furan ring with a carbonyl group (-C(=O)NHNH₂) at the 2-position and an amino group (-NH₂) at the 5-position. The amino group is attached to a dashed line.</p>
Q ²¹	 <p>Chemical structure of 3-amino-4-methoxy-NH-phenylhydrazide with a furan ring. It consists of a furan ring with a carbonyl group (-C(=O)NHNH₂) at the 2-position and an amino group (-NH₂) at the 5-position. The amino group is attached to a dashed line.</p>

Q ²²	 <chem>CC1=CC=C(NC(=O)N)C=C1</chem>
Q ²³	 <chem>CC(C)S(=O)(=O)c1ccc(OC)cc1N</chem>
Q ²⁴	 <chem>NC(=O)c1cc(N)ccc1Cl</chem>
Q ²⁵	 <chem>COc1cc(NC(=O)N)cc(OC)c1</chem>
Q ²⁶	 <chem>NC(=O)c1ccc(N)cc1</chem>

Preferred Q are Q₆, Q₇ and Q₁₀.

Preferably Q is 5-carbamoyl-2-methoxy-phenyl.

Preferably, W is an optionally substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, alkylthio, aralkylthio, carboxyl, carboxylalkyl, esterified carboxyl, alkylsulfonyl, carbo-alkoxy, carbo-aryloxy or heterocyclic group. More preferably, W is an optionally substituted alkyl, alkenyl, alkynyl, aryl or heterocyclic group. A preferred aryl
 5 group is phenyl. A preferred heterocyclic group is an unsaturated heterocyclic group, more preferably a monocyclic unsaturated heterocyclic group.

Where W is a substituted alkyl, alkenyl or alkynyl group, it is preferably substituted with an optionally substituted alkyl, aryl, heterocyclic, $-Y^1$ -alkyl, $-Y^1$ -aryl or $-Y^1$ -(heterocyclic)
 10 group, where Y^1 is O, S or NR^6 (preferably O or S) and R^6 is independently H or alkyl. Where W is a substituted alkyl group, it is more preferably substituted with an optionally substituted aryl (e.g. phenyl), heterocyclic or $-Y^1$ -(heterocyclic) group.

In one embodiment, W is preferably a benzyl group optionally substituted on the phenyl
 15 ring.

Alternatively, where W is a substituted alkyl, alkenyl or alkynyl group, it may be substituted with $-(O\text{-alkylene})_a\text{-O-alkyl}$ (preferably $-(O\text{-ethylene})_a\text{-O-alkyl}$ or $-(O\text{-propylene})_a\text{-O-alkyl}$), where a is from 1 to 20 (preferably 1 to 10, preferably 1 to 5,
 20 more preferably 2).

Where substituted, W is preferably independently substituted by one or more (e.g. 1, 2 or 3) of: halogen; trihalomethyl; $-\text{NO}_2$; $-\text{CN}$; $-\text{Y-C(=Y)-R}^5$; $-\text{C(=Y)-R}^5$; $-\text{C(=Y)-Y-R}^5$; $-\text{Y-C(=Y)-Y-R}^5$; $-\text{SOR}^5$; $-\text{S(=O)}_2\text{R}^5$; $-\text{Y-S(=O)OR}^5$; $-\text{Y-S(=O)}_2\text{R}^5$; $-\text{S(=O)}_2\text{-YR}^5$;
 25 $-\text{Y-S(=O)}_2\text{-YR}^5$; $-\text{R}^5$; $-\text{YR}^5$; or alkyl (preferably methyl) substituted with one or more (e.g. 1, 2 or 3, preferably 1) of halogen, trihalomethyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{Y-C(=Y)-R}^5$, $-\text{C(=Y)-R}^5$, $-\text{C(=Y)-Y-R}^5$, $-\text{Y-C(=Y)-Y-R}^5$, $-\text{SOR}^5$, $-\text{S(=O)}_2\text{R}^5$, $-\text{Y-S(=O)OR}^5$, $-\text{Y-S(=O)}_2\text{R}^5$, $-\text{S(=O)}_2\text{-YR}^5$, $-\text{Y-S(=O)}_2\text{-YR}^5$ or $-\text{YR}^5$. Y is independently O, S or NR^5 , and R^5 is independently H or an optionally substituted alkyl, aryl or heterocyclic group (preferably H
 30 or alkyl). More preferred substituents are halogen, trihalomethyl, $-\text{NO}_2$, $-\text{CN}$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{R}^5$, $-\text{C(=O)H}$, $-\text{C(=O)R}^5$, $-\text{OC(=O)R}^5$, $-\text{OC(=O)OR}^5$, $-\text{C(=O)NH}_2$, $-\text{C(=O)NR}^5_2$, $-\text{N(R}^5\text{)C(=O)R}^5$, $-\text{N(R}^5\text{)C(=O)OR}^5$, $-\text{OC(=O)NR}^5_2$, $-\text{N(R}^5\text{)C(=O)NR}^5_2$, $-\text{C(=S)NH}_2$,

-C(=S)NR⁵₂, -N(R⁵)C(=S)R⁵, -N(R⁵)C(=S)NR⁵₂, -C(=NH)NH₂, -C(=NR⁵)NR⁵₂,
 -N(R⁵)C(=NR⁵)R⁵, -N(R⁵)C(=NR⁵)NR⁵₂, -SOR⁵, -S(=O)₂R⁵, -S(=O)₂OH, -S(=O)₂OR⁵,
 -S(=O)₂NR⁵₂, -N(R⁵)SO₂R⁵, -N(R⁵)SO₂NR⁵₂, -NR⁵₂, -R⁵ or -YR⁵. Still more preferred
 substituents are halogen, -CN, -CO₂H, -CO₂R⁵, -C(=O)R⁵, -C(=O)NH₂, -C(=O)NR⁵₂,
 5 -N(R⁵)C(=O)R⁵, -C(=S)NH₂, -C(=S)NR⁵₂, -C(=NH)NH₂, -C(=NR⁵)NR⁵₂, -S(=O)₂R⁵,
 -NR⁵₂, -R⁵ or -YR⁵.

Where W is a substituted alkyl, alkenyl or alkynyl group (preferably alkyl, preferably
 methyl) substituted with an optionally substituted alkyl (preferably cycloalkyl), aryl,
 10 heterocyclic, -Y¹-alkyl, -Y¹-aryl or -Y¹-(heterocyclic) group, the alkyl, aryl, heterocyclic,
 -Y¹-alkyl, -Y¹-aryl or -Y¹-(heterocyclic) substituent group may optionally be substituted by
 one or more (e.g. 1, 2 or 3) of: halogen; trihalomethyl; -NO₂; -CN; -Y-C(=Y)-R⁵;
 -C(=Y)-R⁵; -C(=Y)-Y-R⁵; -Y-C(=Y)-Y-R⁵; -SOR⁵; -S(=O)₂R⁵; -Y-S(=O)OR⁵;
 -Y-S(=O)₂R⁵; -S(=O)₂-YR⁵; -Y-S(=O)₂-YR⁵; -R⁵; -YR⁵; or alkyl (preferably methyl)
 15 substituted with one or more (e.g. 1, 2 or 3, preferably 1) of halogen, trihalomethyl, -NO₂,
 -CN, -Y-C(=Y)-R⁵, -C(=Y)-R⁵, -C(=Y)-Y-R⁵, -Y-C(=Y)-Y-R⁵, -SOR⁵, -S(=O)₂R⁵,
 -Y-S(=O)OR⁵, -Y-S(=O)₂R⁵, -S(=O)₂-YR⁵, -Y-S(=O)₂-YR⁵ or -YR⁵. Y is independently O,
 S or NR⁵, and R⁵ is independently H or an optionally substituted alkyl, aryl or heterocyclic
 group (preferably H or alkyl). More preferred substituents on the alkyl, aryl, heterocyclic,
 20 -Y¹-alkyl, -Y¹-aryl or -Y¹-(heterocyclic) substituent group are halogen, trihalomethyl,
 -NO₂, -CN, -CO₂H, -CO₂R⁵, -C(=O)H, -C(=O)R⁵, -OC(=O)R⁵, -OC(=O)OR⁵, -C(=O)NH₂,
 -C(=O)NR⁵₂, -N(R⁵)C(=O)R⁵, -N(R⁵)C(=O)OR⁵, -OC(=O)NR⁵₂, -N(R⁵)C(=O)NR⁵₂,
 -C(=S)NH₂, -C(=S)NR⁵₂, -N(R⁵)C(=S)R⁵, -N(R⁵)C(=S)NR⁵₂, -C(=NH)NH₂,
 -C(=NR⁵)NR⁵₂, -N(R⁵)C(=NR⁵)R⁵, -N(R⁵)C(=NR⁵)NR⁵₂, -SOR⁵, -S(=O)₂R⁵, -S(=O)₂OH,
 25 -S(=O)₂OR⁵, -S(=O)₂NR⁵₂, -N(R⁵)SO₂R⁵, -N(R⁵)SO₂NR⁵₂, -NR⁵₂, -R⁵ or -YR⁵. Still more
 preferred substituents are halogen, -CN, -CO₂H, -CO₂R⁵, -C(=O)R⁵, -C(=O)NH₂,
 -C(=O)NR⁵₂, -N(R⁵)C(=O)R⁵, -C(=S)NH₂, -C(=S)NR⁵₂, -C(=NH)NH₂, -C(=NR⁵)NR⁵₂,
 -S(=O)₂R⁵, -NR⁵₂, -R⁵ or -YR⁵.

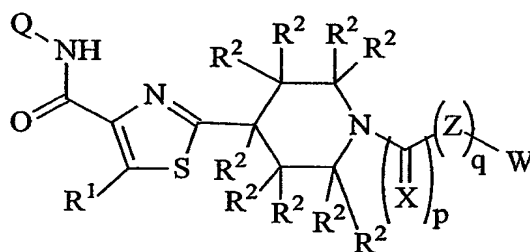
30 Preferably, W comprises an optionally substituted aryl or heterocyclic group. More
 preferably, W is an optionally substituted aryl or heterocyclic group. A preferred aryl

group is phenyl. A preferred heterocyclic group is an unsaturated heterocyclic group, more preferably a monocyclic unsaturated heterocyclic group.

Preferably W is a heterocyclic group, optionally substituted with 1, 2 or 3 substituents, preferably 2 substituents. Preferably W is an optionally substituted phenyl, oxazolyl, diazolyl, quinolinyl, benzofuranyl or pyridinyl. Preferably, the substituents are independently selected from alkoxy, amide, carboxy, carboxylalkyl, alkoxy, cyano, halogen and a heterocyclic group, more preferably, methoxy, cyano, chlorine, oxazolyl, tetrazolyl, oxazolyl substituted with lower alkyl, -C(O)NH₂, -C(O)NHR, -C(O)NR₂,
 10 -C(S)NH₂ and -NHC(O)R, where R is lower alkyl, preferably methyl.

Alternatively, W is an alkyl, alkylene, alkyne, alkoxy or amine, carboxylalkyl, optionally substituted with a heterocyclic group. Preferably, the heterocyclic group is substituted with 1, 2 or 3 substituents independently selected from alkoxy, amide, carboxy, carboxylalkyl, alkoxy, cyano, halogen and a heterocyclic group. More preferably the substituents are methoxy, cyano, chlorine, oxazolyl, tetrazolyl, oxazolyl substituted with lower alkyl, -C(O)NH₂, -C(O)NHR, -C(O)NR₂, -C(S)NH₂ and -NHC(O)R, where R is lower alkyl, preferably methyl.

20 Preferably, the compound of the invention has the formula (III):



formula (III)

25 wherein Q, R¹, R², X, Z, W, p and q are as defined above.

In one embodiment of the invention, the compound of formula (I) is preferably:

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-{1-[(4,7-dimethylpyrazolo[5,1-*c*][1,2,4]triazin-3-yl)carbonyl]-4-piperidinyl}-1,3-thiazole-4-carboxamide;

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-(1-benzofuran-2-ylcarbonyl)-4-piperidinyl]-
5 1,3-thiazole-4-carboxamide;

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-(3-phenyl-2-propynoyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide;

10 2-(1-{[2-(allylsulfanyl)-3-pyridinyl]carbonyl}-4-piperidinyl)-*N*-[5-(aminocarbonyl)-2-methoxyphenyl]-1,3-thiazole-4-carboxamide;

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-{1-[(2-chlorophenyl)acetyl]-4-piperidinyl}-1,3-thiazole-4-carboxamide;

15

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-{1-[(3,4-dimethylphenoxy)acetyl]-4-piperidinyl}-1,3-thiazole-4-carboxamide;

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-({4-(dimethylamino)phenyl}amino)carbonothioyl]-4-piperidinyl]-1,3-thiazole-4-carboxamide;

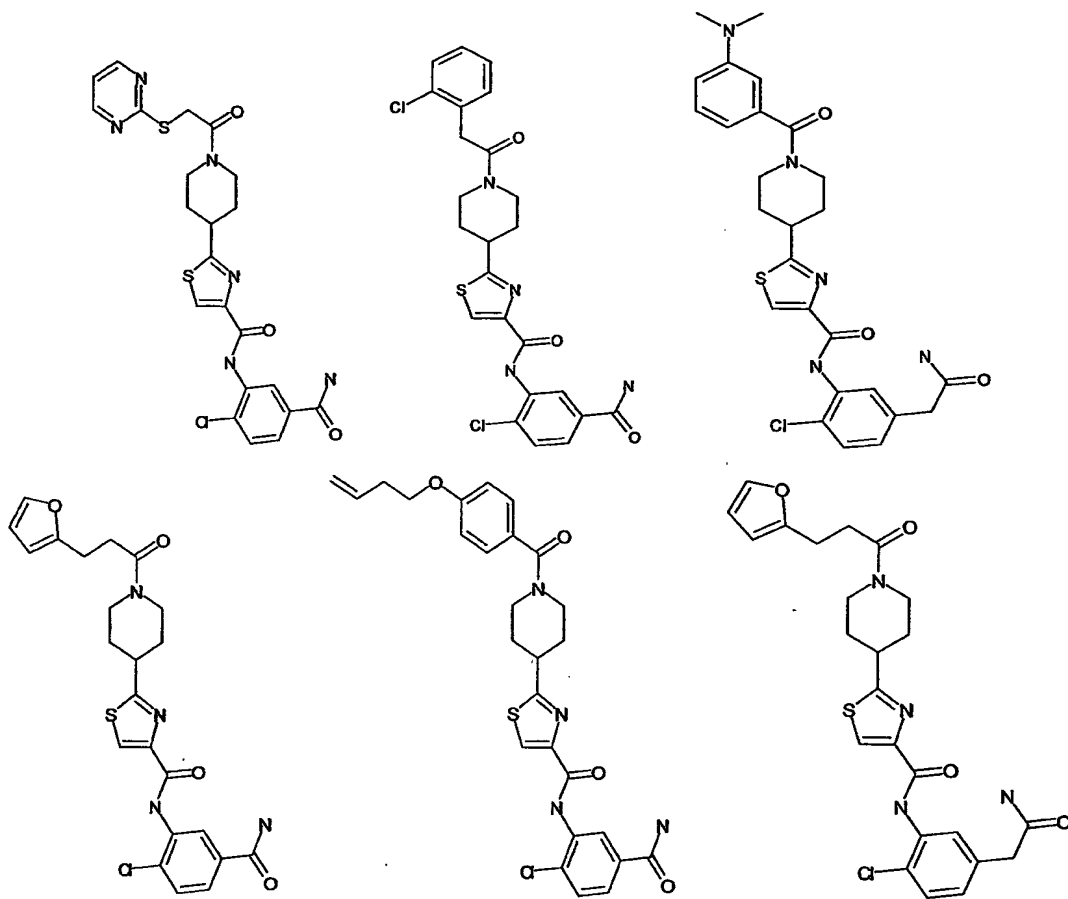
20

or

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-(1-{[4-(2-pyridinyl)-1-piperazinyl]carbonyl}-4-piperidinyl)-1,3-thiazole-4-carboxamide.

25

More preferred compounds of the invention are:



According to a further aspect of the present invention there is provided a compound of the
5 present invention for use in a method of treatment of disease.

The compounds of the present invention may preferably be employed in the treatment of VEGF-mediated disorders such as endometriosis, various malignant and non-malignant tumours, psoriasis and other skin conditions, atheromatous disease, rheumatoid arthritis,
10 macular degeneration and the complications of diabetes including retinopathy, nephropathy and neuropathy.

According to a further aspect of the present invention there is provided a compound of the present invention for use in therapy or diagnosis.

According to a further aspect of the present invention there is provided the use of a compound of the present invention for use in the manufacture of a medicament for treating a VEGF-mediated disorder, preferably endometriosis or malignant tumours.

- 5 According to a further aspect of the present invention there is provided a method of treating a disease mediated by VEGF, such as endometriosis, comprising administering to a patient in need of such treatment an effective dose of a compound of the present invention.

- 10 According to a further aspect of the present invention there is provided the use of a VEGF inhibitor for the manufacture of a medicament for treating acute macular degenerative disorder. Preferably, the VEGF inhibitor is a compound of the invention.

- 15 According to a further aspect of the present invention there is provided a method of treating acute macular degenerative disorder comprising administering to a patient in need of such treatment an effective dose of a VEGF inhibitor. Preferably, the VEGF inhibitor is a compound of the invention.

- 20 According to a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound of the present invention in combination with a pharmaceutically acceptable excipient.

- 25 According to a further aspect of the present invention there is provided a VEGF inhibitor for topical administration for the treatment of acute macular degenerative disorder. Preferably, the VEGF inhibitor is a compound of the invention.

- According to a further aspect of the present invention there is provided a topical system for the treatment of acute macular degenerative disorder comprising a VEGF inhibitor. Preferably, the VEGF inhibitor is a compound of the invention.

- 30 The agents described could be used alone or conjointly with treatments such as anti-hormone therapy, surgery, radiotherapy or chemotherapy.

Compounds of the present invention may be administered in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for topical use including transmucosal and transdermal use, for example a cream, ointment, gel, aqueous or oil solution or suspension, salve, patch, plaster or as a component of a lubricant for a condom; 5 for nasal use, for an example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example a finely divided powder or a liquid aerosol; for intra-ocular, sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oil solution or suspension, or incorporated in a 10 biodegradable polymer. In general the above compositions may be prepared in a conventional manner using convention excipients, using standard techniques well known to those skilled in the art of pharmacy. The preferred modes of administration of the compound are oral or intravaginal. Oral administration is particularly preferred.

15 For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules or as an aqueous solution or suspension.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, 20 sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as 25 glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

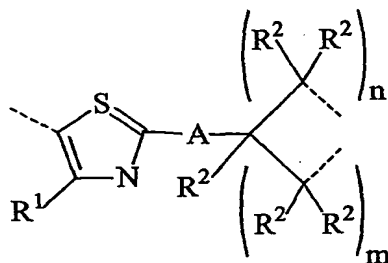
30

For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to

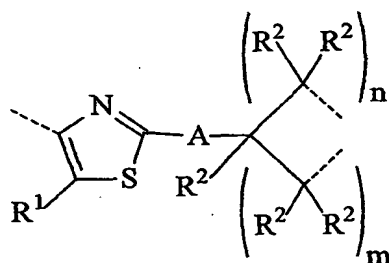
- an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous
- 5 suspensions include ethyl and n-propyl p-hydroxybenzoate. The compounds of the invention may also be provided in a biodegradable polymer, for example for use in conjunction with stents in surgery (e.g. adsorbed on a stent or applied directly to the site of the procedure for slow release of the active agent).
- 10 Topical administration is also a preferred administration. Topical administration, including transmucosal and transdermal use, includes administration by, for example, a cream, ointment, gel, aqueous or oil solution or suspension, salve, patch, plaster, tampon, sanitary napkin, or as a component of a lubricant for a condom. Topical systems include: compositions comprising a VEGF inhibitor in combination with a pharmaceutically
- 15 acceptable excipient for topical administration; and administration devices including a composition comprising a VEGF inhibitor in combination with a pharmaceutically acceptable excipient for topical administration. Examples of compositions comprising a VEGF inhibitor in combination with a topically acceptable excipient are creams, ointments, gels, aqueous or oil solutions or suspensions, or salves. Examples of
- 20 administration devices including a composition comprising a VEGF inhibitor in combination with a topically acceptable excipient are patches, plasters, tampons or sanitary napkins including the composition or condoms including a lubricant comprising the composition.
- 25 It will be appreciated that the dosage levels used may vary over quite a wide range depending upon the compound used, the severity of the symptoms exhibited by the patient and the patient's body weight. Without limitation to the present invention, typical dosages for treatment of endometriosis may be, for example, of the order of 1 microgram/kg/day to 1 milligram/kg/day, more preferably 10 microgram/kg/day to 0.25 milligram/kg/day orally. For
- 30 intra-ocular administration, typical dosages would be of the order of 10 nanogram/kg/day to 1 microgram/kg/day. For treatment of tumours up to 5 milligrams/kg/day would be preferable.

For intra-vaginal administration typical dosages would be 10 micrograms/kg/day to 0.25 milligrams/kg/day.

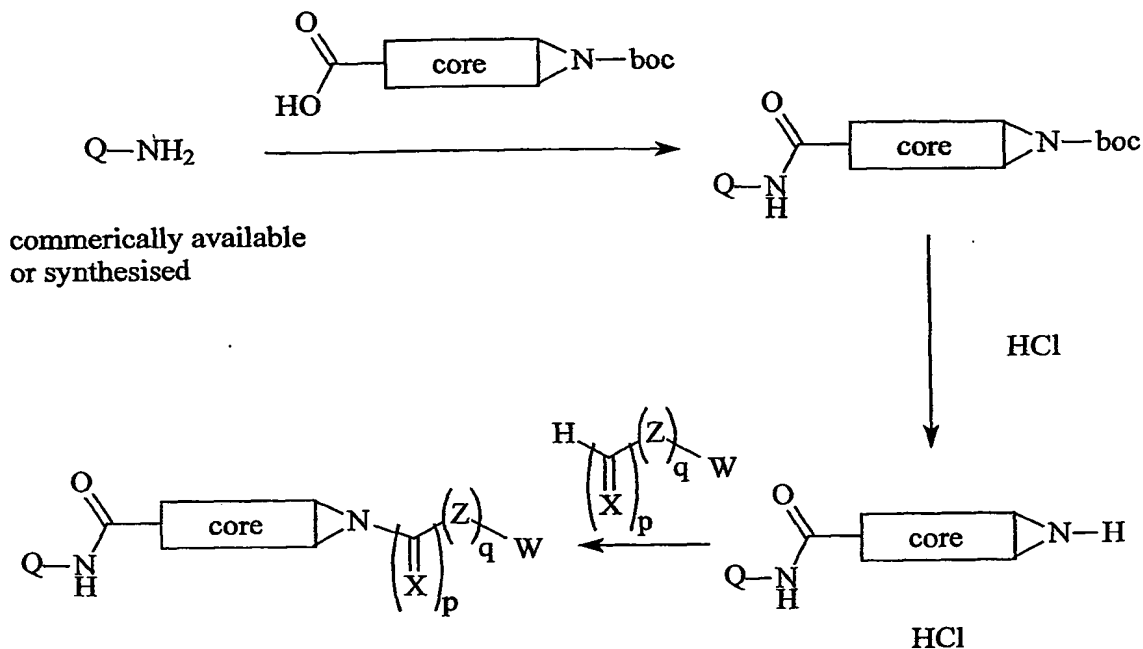
Compounds of this invention may be prepared by the general reaction scheme, Reaction
5 Scheme 1, wherein by "core" is meant the radical



or



Reaction Scheme 1



5 The invention is now further illustrated by means of the following Examples.

Examples

Synthesis of Specific Compounds of the Invention

10

Examples 1-6

Preparation of *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-{1-[(4,7-dimethylpyrazolo[5,1-*c*][1,2,4]triazin-3-yl)carbonyl]-4-piperidinyl}-1,3-thiazole-4-carboxamide; *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-(1-benzofuran-2-ylcarbonyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide; *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-(3-phenyl-2-propynoyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide; 2-(1-{[2-(allylsulfanyl)-3-pyridinyl]carbonyl}-4-piperidinyl)-*N*-[5-(aminocarbonyl)-2-methoxyphenyl]-1,3-thiazole-4-carboxamide; *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-{1-[(2-chlorophenyl)acetyl]-4-piperidinyl}-1,3-thiazole-4-carboxamide; and *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-{1-[(3,4-dimethylphenoxy)acetyl]-4-piperidinyl}-1,3-thiazole-4-carboxamide.

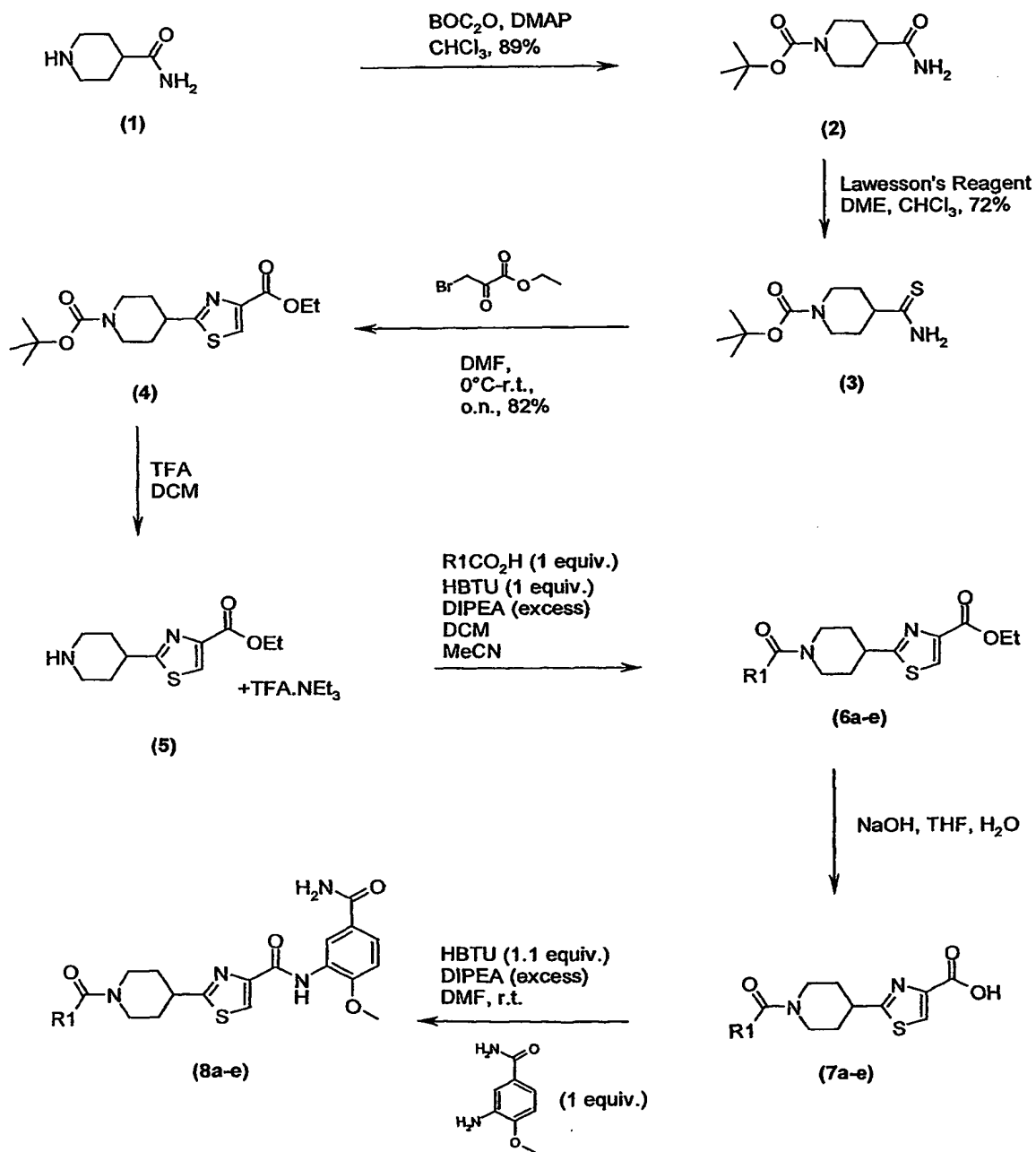
15

20

The above-mentioned compounds were synthesised by Reaction Scheme 2 below:

Reaction Scheme 2

5



4-Carbamoyl-piperidine-1-carboxylic acid *tert*-butyl ester (2)

Isonipecotamide (1) (28.8 g, 0.22 mol) was suspended in chloroform (288 mL). To this was added 4-(dimethylamino)pyridine (DMAP) (23 mg, catalytic) followed by dropwise addition of a solution of BOC-anhydride (56 g, 0.26 mol, 1.14 equiv.) in chloroform (57 mL). The solution was stirred at room temperature for 1 h and then partitioned between chloroform and 10% citric acid solution. The organic phase was washed with citric acid solution and back extracted with chloroform. The combined organic extracts were washed with water, 10% brine and dried (MgSO₄). Filtration followed by evaporation of the filtrate gave the crude product as a pink solid. Crystallisation from ethyl acetate/hexane gave the title compound (2) as a colourless solid in 4 crops (45.5 g, 0.20 mol, 89%), m.p. 159-161°C (lit. 154-156°C).

4-Thiocarbamoyl-piperidine-1-carboxylic acid *tert*-butyl ester (3)

4-Carbamoyl-piperidine-1-carboxylic acid *tert*-butyl ester (2) (45.4 g, 0.199 mol), Lawesson's reagent (40.2 g, 0.099 mol, 0.5 equiv), 1,2-dimethoxyethane (DME) (500 mL) and chloroform (200 mL) were combined and stirred at room temperature. The course of the reaction was followed by tlc analysis (30% ethyl acetate/hexane) and on completion the reaction mixture was evaporated to dryness (glassy solid). The solid was dissolved in ethyl acetate and washed with half saturated potassium carbonate solution, dried (MgSO₄), filtered and concentrated to yield the title compound as a colourless solid. The crude product was crystallised from ethyl acetate and hexane to give the title compound (3) (35 g, 0.14 mol, 72%).

4-(4-Ethoxycarbonyl-thiazol-2-yl)-piperidine-carboxylic acid *tert*-butyl ester (4)

4-Thiocarbamoyl-piperidine-1-carboxylic acid *tert*-butyl ester (3) (25 g, 102 mmol) was dissolved in anhydrous *N,N*-dimethylformamide (DMF) (125 mL) and cooled to 0°C in an ice-bath. A solution of ethyl bromopyruvate (22.2 g, 14.3 mL, 114 mmol, 1.1 equiv) in anhydrous DMF (125 mL) was added dropwise with stirring. The reaction mixture was allowed to warm slowly to room temperature and stirred overnight. Triethylamine (25 mL)

was added dropwise with stirring at the rate of 1 mL/g of thioamide used. The DMF was removed *in vacuo* keeping the temperature below 60°C. The resulting residue was partitioned between ethyl acetate (75 mL) and brine (100 mL). Sufficient water was added to ensure complete dissolution of the precipitated salts in the aqueous phase. The aqueous
5 phase was extracted twice with ethyl acetate and the combined organic extracts washed successively with brine (x2), water (x2) and brine (x2). The organic phase was simultaneously dried with MgSO₄ and decolourised with finely divided charcoal. The mixture was filtered through Celite and concentrated *in vacuo* to give a yellow oil. Trituration with hexane yielded a yellow solid. This was diluted with an excess of hexane
10 and cooled overnight to allow complete crystallisation of product. The product was collected by filtration, washed with hexane and dried *in vacuo* at room temperature. Recrystallisation from IPA/water gave the title compound (4) (28.33 g, 83 mmol, 82%).

2-Piperidine-4-yl-thiazole-4-carboxylic acid ethyl ester (5)

15

To a solution of 4-(4-ethoxycarbonyl-thiazol-2-yl)-piperidine-carboxylic acid *tert*-butyl ester (4) (5 g, 14.7 mmol) in dichloromethane (20 mL) at 0°C was added neat trifluoroacetic acid (TFA) (17 mL, 221 mmol, 15 equivalents) dropwise with stirring, under an inert atmosphere. On completion of addition the reaction mixture was allowed to
20 warm to room temperature and stirring continued until deprotection complete (typically 3 hours, monitored by tlc, 1:1 hexane/ethyl acetate). On completion of reaction the mixture was concentrated *in vacuo* to remove TFA. Toluene (dioxan for (6f)) was then added and re-concentrated to further remove TFA - this was repeated 2-3 times to ensure maximum removal of TFA. The product was further dried *in vacuo* overnight to remove the last
25 traces of TFA. The TFA salt of the free amine was dissolved in dichloromethane (10 mL), cooled to 0°C in an ice bath and treated with triethylamine (6.15 mL, 3 equiv). It was assumed a quantitative conversion of BOC-protected (4) to free amine (5).

Compounds (6a-e)

30

To a solution of 2-piperidine-4-yl-thiazole-4-carboxylic acid ethyl ester (5) (14.7 mmol) in dichloromethane (10 mL) at 0°C was added acetonitrile (40 mL). To this solution was

sequentially added the acid to be reacted (R_1COOH – see Table 2) (14.7mmol, 1 equiv.), N,N,N',N' -tetramethyl-O-(1*H*-benzotriazole-1-yl) uronium hexafluorophosphate (HBTU) (14.7mmol, 5.57g, 1 equiv.), and N,N -diisopropylethylamine (DIPEA) (7.7 mL, 3 equiv.). The reaction mixture was stirred at room temperature for 48 h to allow for completion of
 5 reaction. After this time the reaction mixture was concentrated *in vacuo* to remove the solvent and the residue was suspended in dichloromethane (80 mL) and washed with brine (2 x 50 mL), water (50 mL), 10% citric acid (50 mL), brine, saturated sodium bicarbonate solution (50 mL) and finally brine. The organic layer was dried over $MgSO_4$ and treated with decolourising charcoal, filtered and concentrated *in vacuo*.

10

Table 2

id	R_1CO_2H	yield
6a	2-chlorophenylacetic acid	not purified
6b	3,4-dimethylphenoxyacetic acid	not purified
6c	1-benzofuran-2-carboxylic acid	65% (after chromatography)
6d	3-phenylpropynic acid	not purified
6e	2-(allylthio)nicotinic acid	not purified
6f	4,7-dimethylpyrazolo[5,1-c][1,2,4]triazine-3-carboxylic acid	not purified

Compounds (7a-e)

15

Compound (6a-e) (13mmol) was dissolved in THF (35 mL) and water (23 mL) and cooled to 0°C. A solution of sodium hydroxide (1.04g, 26mmol, 2 equiv.) in water (20 mL) was added dropwise with stirring. The reaction was monitored by tlc analysis and when complete (typically 2 h) the reaction mixture was diluted with brine (30 mL) and washed
 20 with ether (100 mL). The reaction mixture was acidified using 20% citric acid solution. The acidic mixture was then extracted with a suitable organic solvent (dichloromethane or ethyl acetate) and when fully extracted the organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield essentially pure product.

Table 3

id	extraction solvent	yield
7a	ethyl acetate	58% (over two steps)
7b	ethyl acetate	61% (over two steps)
7c	ethyl acetate	80%
7d	dichloromethane	41% (over two steps)
7e	ethyl acetate	54% (over two steps)
7f	ethyl acetate	53% (over two steps)*

*product was isolated by repeated crystallisation from ethyl acetate

5

Compounds (8a-e)

Compound (7a-e) was dissolved in anhydrous DMF (0.58 M solution). 3-Amino-4-methoxybenzamide was dissolved in 10% DIPEA and anhydrous DMF (0.58 M solution).
10 HBTU was dissolved in anhydrous DMF (0.64 M solution). The amine solution (0.3 mL, 0.175 mmol) was dispensed into an individual well in a 2.2 mL deep well plate using a Packard MPII robot. An Eppendorf multi-dispenser was used to dispense the acid solution (0.3 mL, 0.175 mmol, 1 equiv) and then to dispense the HBTU solution (0.3 mL, 0.19 mmol, 1.1 equiv). A further portion of DIPEA (0.05 mL) was added to the well, which
15 was capped and shaken on an orbital shaker overnight. The reaction mixture was concentrated *in vacuo* (Genevac). The residue was dissolved in dichloromethane (1 mL) and given a sequence of aqueous washes using the MPII robot: 0.5 N HCl (0.7 mL), 10% potassium carbonate solution (0.7 mL) then water (0.7 mL). Finally the dichloromethane extract (0.7 mL) containing the product was concentrated and dried (Genevac) to constant
20 mass.

Table 4

id	RRcode	DAD (254 nm)	ES+
8a	1506-03737	100%	513
8b	1506-03914	97%	523
8c	1506-01284	88%	505
8d	1506-01461	90%	489
8e	1506-02331	89%	538
8f	1506-00581	86%	535

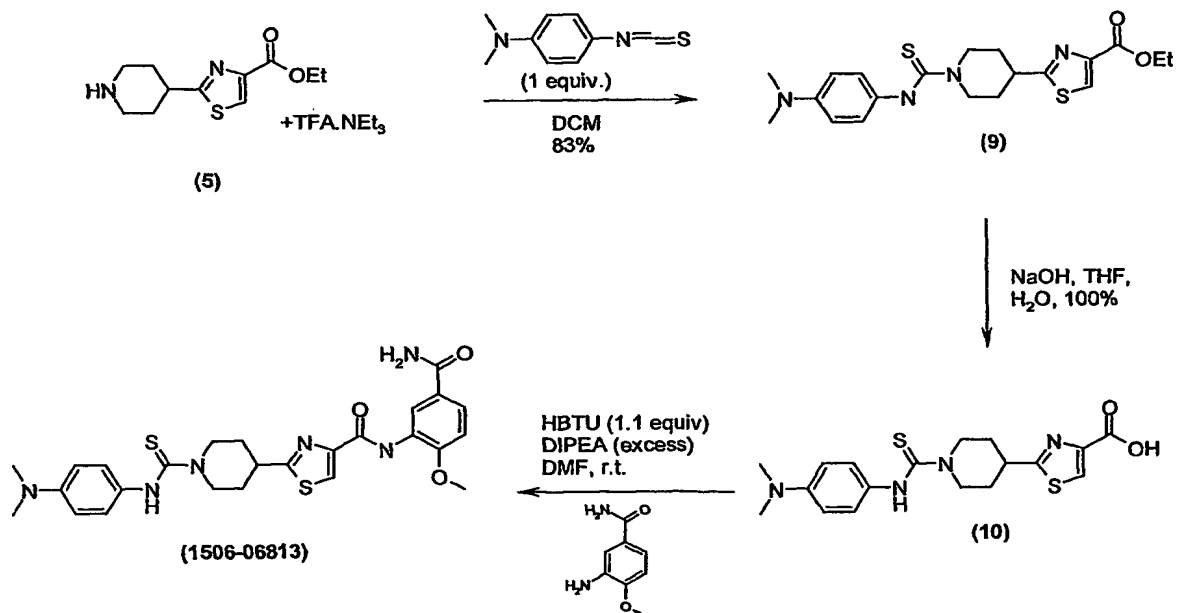
Example 7

- 5 Preparation of *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-([4-(dimethylamino)phenyl]amino)carbonothioyl]-4-piperidiny]-1,3-thiazole-4-carboxamide;

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-([4-(dimethylamino)phenyl]amino)carbonothioyl]-4-piperidiny]-1,3-thiazole-4-carboxamide

- 10 was prepared by the synthetic route set out in Reaction Scheme 3 below.

Reaction Scheme 3



2-[1-(4-Dimethylamino-phenylthiocarbamoyl)-piperidine-4-yl]-thiazole-4-carboxylic acid ethyl ester (9)

To a solution of 2-piperidine-4-yl-thiazole-4-carboxylic acid ethyl ester (5) (14.7 mmol) in dichloromethane (10 mL) at 0°C was added dichloromethane (80 mL). To this was added 4-(dimethylamino)phenylisothiocyanate (14.7mmol, 1 equiv.). The reaction mixture was stirred at room temperature for 48 h to allow for completion of reaction. After this time the reaction mixture was diluted with dichloromethane (100 mL) and washed with water (2 x 100 mL) and brine (50 mL). The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo* to yield the thiourea in 83% yield following chromatography.

2-[1-(4-Dimethylamino-phenylthiocarbamoyl)-piperidine-4-yl]-thiazole-4-carboxylic acid (10)

2-[1-(4-Dimethylamino-phenylthiocarbamoyl)-piperidine-4-yl]-thiazole-4-carboxylic acid ethyl ester (9) (13 mmol) was dissolved in THF (35 mL) and water (23 mL) and cooled to 0°C. A solution of sodium hydroxide (1.04g, 26 mmol, 2 equiv.) in water (20 mL) was added dropwise with stirring. The mixture was stirred for 2 h at r.t. The mixture was diluted with brine (30 mL) and washed with ether (100 mL). The reaction mixture was acidified using 20% citric acid solution. The acidic mixture was extracted with ethyl acetate and when fully extracted the organic extracts were combined, dried over MgSO₄, filtered and concentrated *in vacuo* to yield the title compound (10) in quantitative yield.

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-({[4-(dimethylamino)phenyl]amino}carbonothioyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide

2-[1-(4-Dimethylamino-phenylthiocarbamoyl)-piperidine-4-yl]-thiazole-4-carboxylic acid (10) was dissolved in anhydrous DMF (0.58 M solution). 3-Amino-4-methoxybenzamide was dissolved in 10% DIPEA and anhydrous DMF (0.58 M solution). HBTU was dissolved in anhydrous DMF (0.64 M solution). The amine solution (0.3 ml, 0.175 mmol) was dispensed into an individual well in a 2.2 mL deep well plate using a Packard MPII

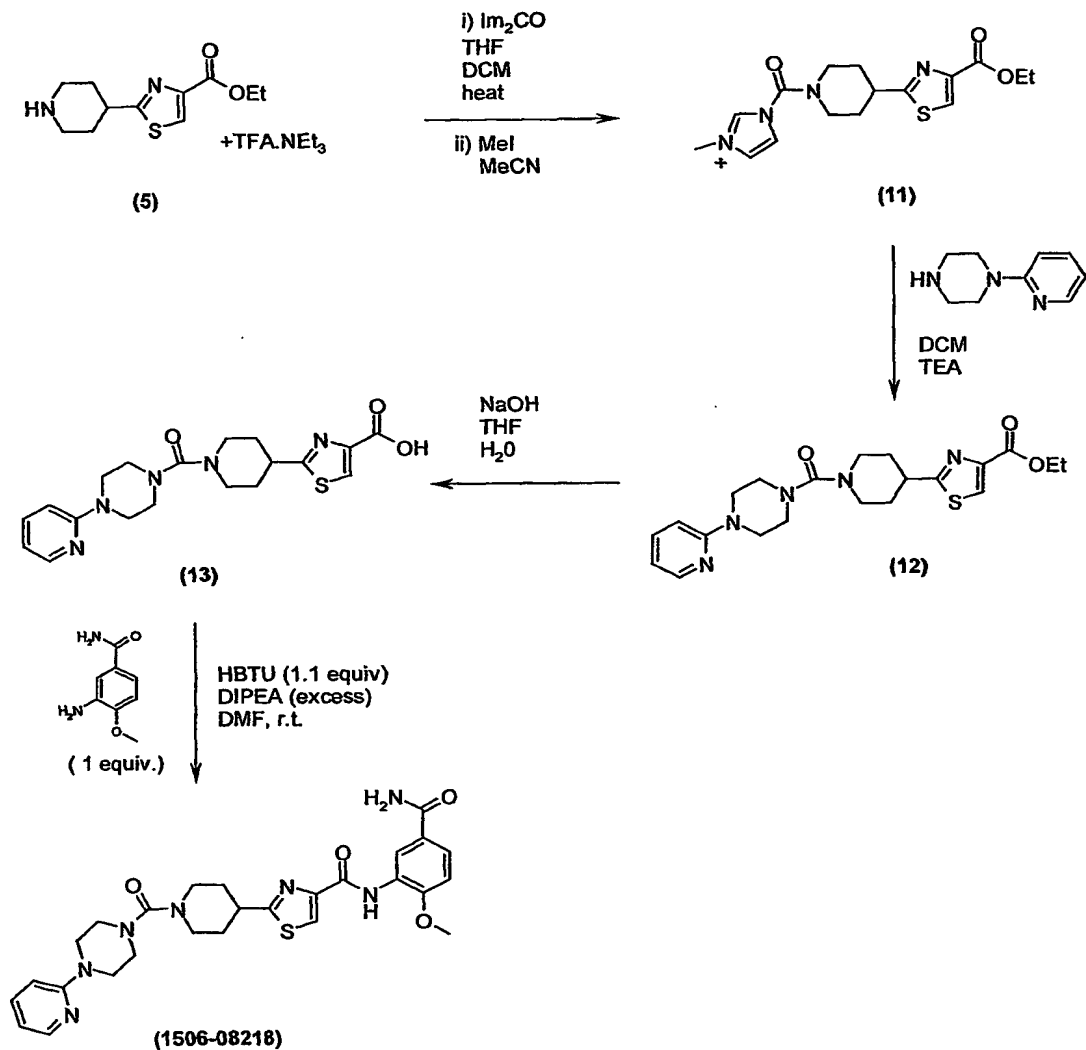
robot. An Eppendorf multi-dispenser was used to dispense the acid solution (0.3 mL, 0.175 mmol, 1 equiv) and then to dispense the HBTU solution (0.3 mL, 0.19 mmol, 1.1 equiv). A further portion of DIPEA (0.05 mL) was added to the well, which was capped and shaken on an orbital shaker overnight. The reaction mixture was concentrated *in vacuo* (Genevac). The residue was dissolved in dichloromethane (1 mL) and given a sequence of aqueous washes using the MP11 robot: 0.5 N HCl (0.7 mL), 10% potassium carbonate solution (0.7 mL) then water (0.7 mL). Finally the dichloromethane extract (0.7 mL) containing the product was concentrated and dried (Genevac) to constant mass to give *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-({[4-(dimethylamino)phenyl]amino}carbonothioyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide (DAD 75% (254nm), ES+ 539).

Example 8

Preparation of *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-(1-{[4-(2-pyridinyl)-1-piperazinyl]carbonyl}-4-piperidinyl)-1,3-thiazole-4-carboxamide

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-(1-{[4-(2-pyridinyl)-1-piperazinyl]carbonyl}-4-piperidinyl)-1,3-thiazole-4-carboxamide was prepared by the synthetic route set out in Reaction Scheme 4 below.

Reaction Scheme 4



5 3-[4-(4-Ethoxycarbonyl-thiazol-2-yl)-piperidine-1-carbonyl]-1-methyl-3H-imidazol-1-ium (11)

A solution of 2-piperidine-4-yl-thiazole-4-carboxylic acid ethyl ester (5) (14.7 mmol) in dichloromethane (15 mL) was added dropwise to a suspension of carbonyldiimidazole in tetrahydrofuran (15 mL). The mixture was heated at reflux overnight then cooled to room temperature. The solvent was removed in vacuo and the residue was dissolved in dichloromethane (80 mL), washed with water and dried over MgSO_4 and concentrated in

vacuo. The residue was dissolved in acetonitrile and methyl iodide added (59 mmol). The mixture was stirred overnight and concentrated to give the title compound which was used without purification.

5 **2-[1-(4-Pyridine-2-yl-piperazine-1-carbonyl)-piperidin-4-yl]-thiazole-4-carboxylic acid ethyl ester (12)**

3-[4-(4-Ethoxycarbonyl-thiazol-2-yl)-piperidine-1-carbonyl]-1-methyl-3*H*-imidazol-1-ium (11) was taken up in dichloromethane (75 mL) and 1-(2-pyridyl)piperazine (14.7 mmol, 1
10 equiv.) and triethylamine (14.7 mmol, 1 equiv.) added. The mixture was stirred overnight and diluted with dichloromethane. The mixture was washed with water and brine, dried and concentrated *in vacuo* to yield the title compound which was used without purification.

15 **2-[1-(4-Pyridine-2-yl-piperazine-1-carbonyl)-piperidin-4-yl]-thiazole-4-carboxylic acid ethyl ester (13)**

The ethyl ester (12) was taken up in tetrahydrofuran (40 mL) / water (20 mL) and sodium hydroxide (29.4 mmol) in water (20 mL) added. The mixture was stirred for 2 h at room temperature. The mixture was then extracted with ether and the aqueous phase acidified
20 with 10% citric acid solution. The aqueous phase was extracted with ethyl acetate and the combined extracts washed with brine, dried and concentrated *in vacuo*. Precipitated product remaining in the aqueous layer was filtered, dried and added to the residue. The title compound (13) was obtained as a colourless solid [total yield 59% (3 steps)].

25 ***N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-(1-{[4-(2-pyridinyl)-1-piperazinyl]carbonyl}-4-piperidinyl)-1,3-thiazole-4-carboxamide**

2-[1-(4-Pyridine-2-yl-piperazine-1-carbonyl)-piperidin-4-yl]-thiazole-4-carboxylic acid ethyl ester (13) was dissolved in anhydrous DMF (0.58 M solution). 3-Amino-4-
30 methoxybenzamide was dissolved in 10% DIPEA and anhydrous DMF (0.58 M solution). HBTU was dissolved in anhydrous DMF (0.64 M solution). The amine solution (0.3 mL, 0.175 mmol) was dispensed into an individual well in a 2.2 mL deep well plate using a

Packard MPII robot. An Eppendorf multi-dispenser was used to dispense the acid solution (0.3 mL, 0.175 mmol, 1 equiv) and then to dispense the HBTU solution (0.3 mL, 0.19 mmol, 1.1 equiv). A further portion of DIPEA (0.05 mL) was added to the well, which was capped and shaken on an orbital shaker overnight. The reaction mixture was concentrated *in vacuo* (Genevac). The residue was dissolved in DCM (1 mL) and given a sequence of aqueous washes using the MPII robot: 0.5 N HCl (0.7 mL), 10% potassium carbonate solution (0.7 mL) then water (0.7 mL). Finally the DCM extract (0.7 mL) containing the product was concentrated and dried (Genevac) to constant mass to give *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-(1-{[4-(2-pyridinyl)-1-piperazinyl]carbonyl}-4-piperidinyl)-1,3-thiazole-4-carboxamide (DAD 100% (254nm), ES+ 550).

Activity Assays

Activities of compounds of the invention were tested using the following assays. The results of the assays are set out in tables 5 and 6 below. For some compounds the assays were repeated to give the multiple results shown in the table.

Initially the compounds were assayed for inhibition of VEGF in a medium throughput ELISA assay before detailed assessment in the HUVEC and VEGF binding assays in examples in 9 and 10. The data from this initial assessment is presented in table 5 in the column labelled "Inhibition %".

Example 9 - Human umbilical vein endothelial cells (HUVEC) proliferation assay

The HUVEC assay measures the potency of test substances to inhibit *in vitro* proliferation of human umbilical vein endothelial cells (HUVEC) when co-stimulated with recombinant human vascular endothelial growth factor (rhVEGF).

HUVEC are grown under defined conditions (EGM-2 medium, 37°C, 5 % CO₂ and 95 % humidity). They are seeded into 48-well plates using EBM medium with only 1 % serum and incubated for 24 h. This is to ensure that cells are not stimulated before treatment with VEGF and test compound.

Test compounds are diluted in medium to concentrations between 0.05 and 50 μ M and dosed together with VEGF₁₆₅ at 12 ng/ml. This VEGF concentration was determined in a VEGF-dose-response curve to be just sub-optimal for maximum cell proliferation. Cells
5 are incubated for 48 h at above conditions and viable cell density is measured using a tetrazolium compound (MTS). Viable cells reduce MTS into a soluble formazan product, which has an absorbance maximum at 490 nm. The absorbance is directly proportional to cell density.

- 10 Control values are: EBM + 1 % serum (no VEGF) \Rightarrow Minimum or Blank
EBM + 1 % serum (12 ng/ml) \Rightarrow Maximum

Example 10 - VEGF-binding ELISA

- 15 The potency of test substances as a VEGF-neutralising moiety is measured in an ELISA format. This assay measures the solution-phase interaction between rhVEGF₁₆₅-biotin and test sample. Unbound VEGF₁₆₅-biotin is then immobilised on a solid-phase anti-hVEGF antibody (R&D systems MAB293). The biotin signal is detected with streptavidin-alkaline
20 phosphatase, which gives a colorimetric signal when incubated with p-nitrophenyl phosphate. Plates are read in a spectrophotometer at 405 nm.

Any test compound that binds to VEGF₁₆₅-biotin and prevents it from binding to the antibody will lower the color signal and be recognized as a "hit". Hits were defined as compounds that show > 60 % inhibition.

25

- Control values are: VEGF₁₆₅-biotin + assay buffer \Rightarrow 0 % inhibition
Soluble VEGF receptor (sflt @ 4 nM) \Rightarrow 70 % inhibition

- The primary screening of all library compounds was done at a compound concentration of
30 50 μ M, followed by measuring dose-response effects of "hits" between 0.05 and 500 μ M for the calculation of IC₅₀ values.

The compounds were dissolved in DMSO and it was shown that the solvent has no effect on the assay at this concentration.

Example 11 – Additional Assays

5

Compounds 1633-00382 and 1633-02177 were tested for selectivity by determining their effect on the following assays:

- 10 • Basic Fibroblast Growth Factor (FGF)-Induced cell proliferation (Gospodarowicz D, Brown KD, Birdwell CR & Zetter BR (1978) J. Cell. Biol. 77: 774-788);
- Epidermal Growth Factor (EGF) radioligand binding assay (Dittadi R, Gion M, Brazzale A., Bruscagnin G. (1990) Clin. Chem. 36: 849-854; Massague J (1983) J. Biol. Chem. 258: 13614-13620); and
- 15 • Platelet-Derived Growth Factor (PDGF) radioligand binding assay (Williams LT, Tremble PM, Lavin MF & Sunday ME (1984) J. Biol. Chem. 259 5287-5294

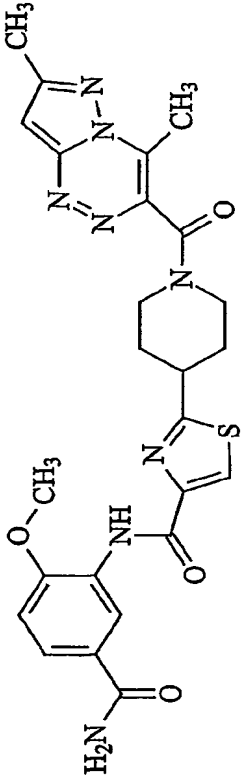
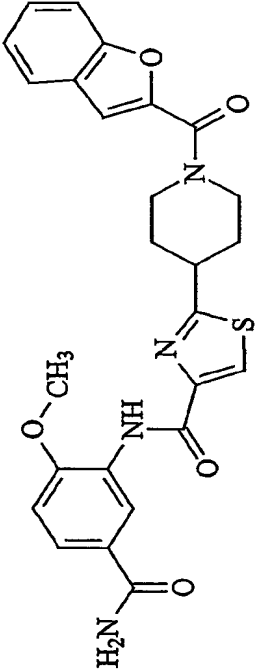
Compounds 1633-00382 and 1633-02177 did not inhibit EGF and PDGF binding to human
20 A431 and mouse 3T3 cells respectively.

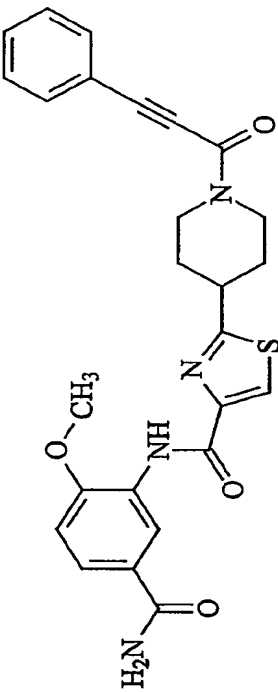
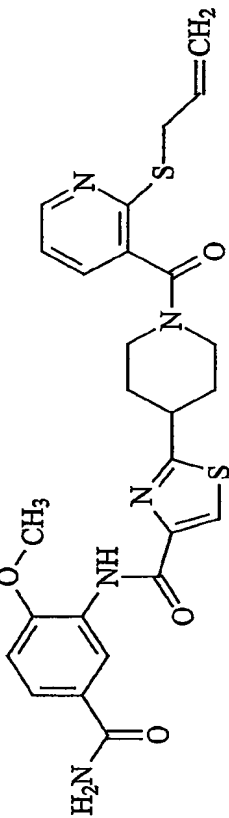
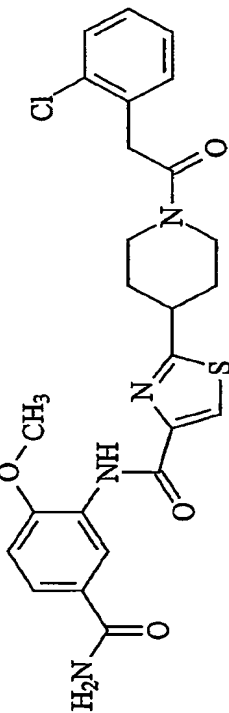
In addition, compound 1633-02177 demonstrated significant anti-proliferative activity against basic FGF with an estimated value of 0.406 μ M. This activity was accompanied by a moderate but not significant cytotoxicity at 10 μ M.

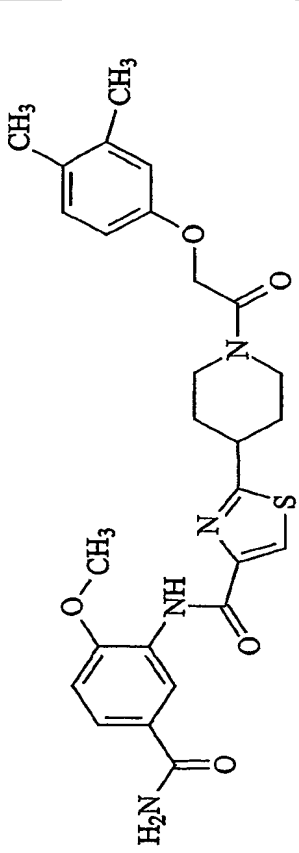
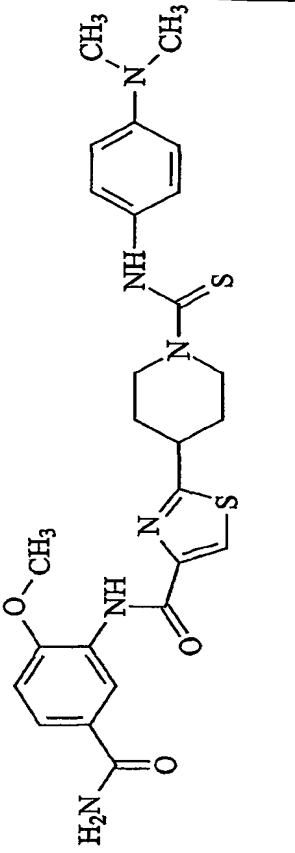
25

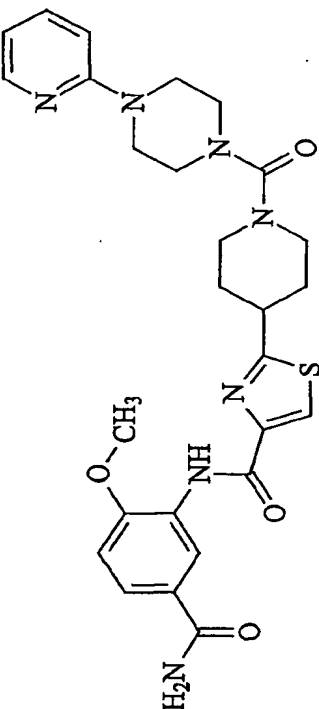
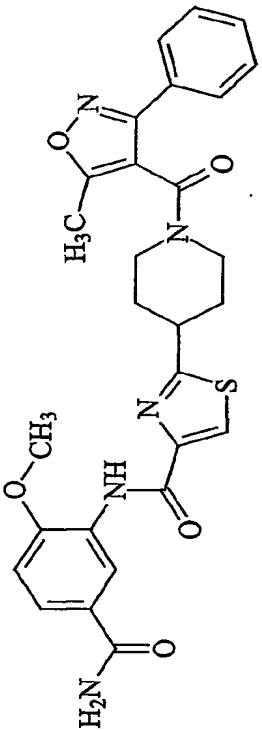
All documents cited herein are incorporated by reference in their entirety.

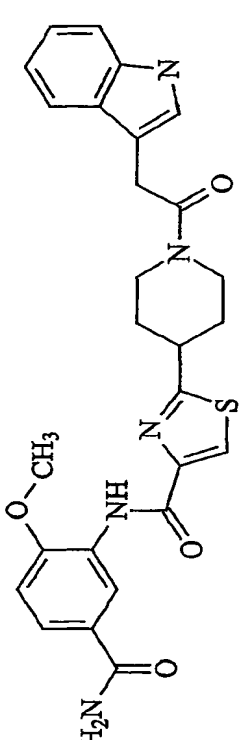
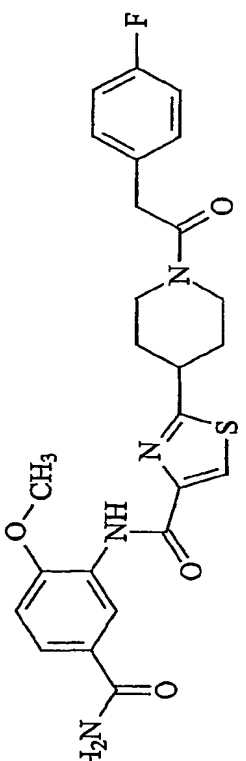
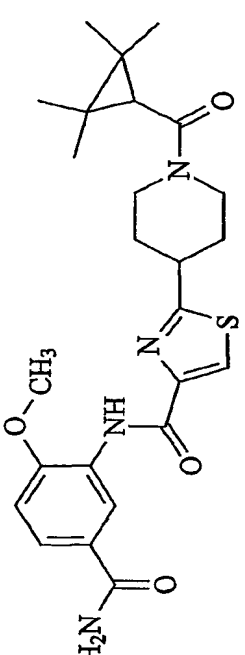
Table 5
Activities of compounds of the invention

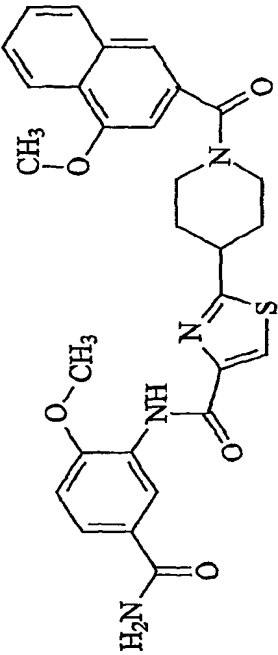
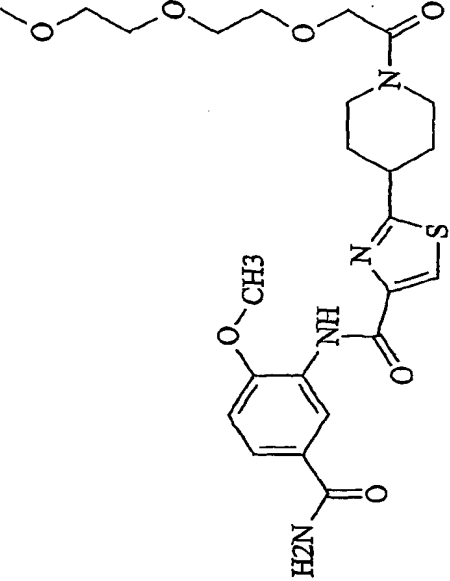
Compound no.	Metris ID no.	Inhibition (%)	IC50 VEGF (μ M)	IC50 HUVEC (μ M)	Structure
1506-00581	M2025-0001	88	4.4	30	
			5.0	31	
1506-01284	M2025-0002	85	11.0	10.1	
			13.5	12.6	

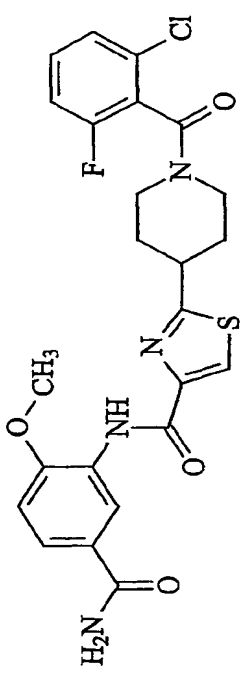
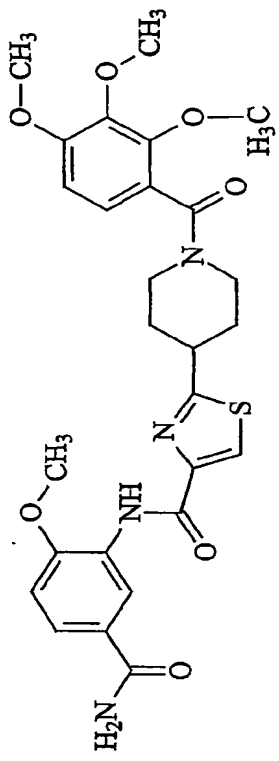
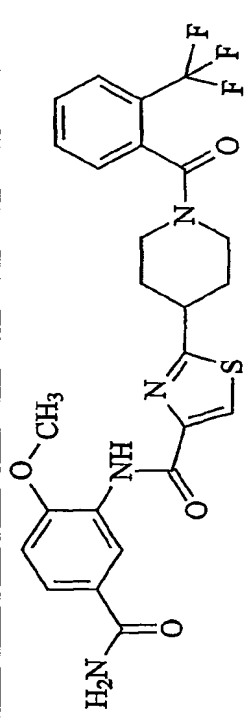
Compound no.	Metris ID no.	Inhibition (%)	IC50 VEGF (μM)	IC50 HUVEC (μM)	Structure
1506-01461	M2025-0003	88 75 83	4	11	
1506-02331	M2025-0004	43 73 79	6.5	22.8	
1506-03737	M2025-0005	60 70 74	214 8	9	

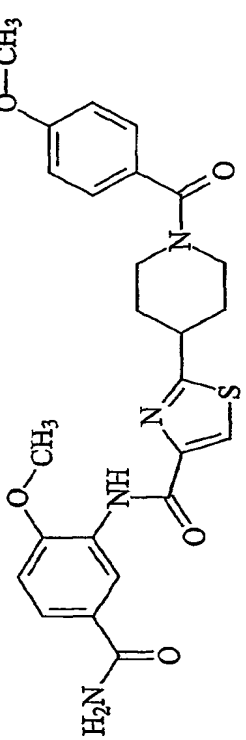
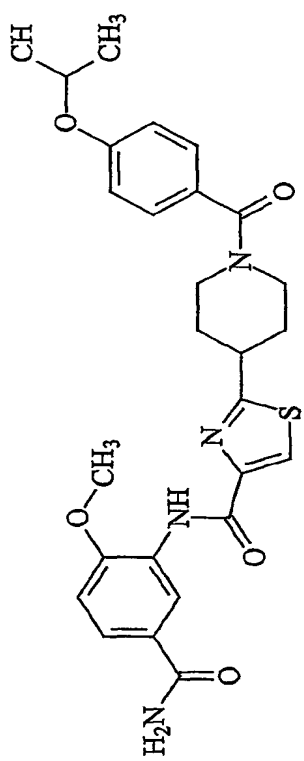
Compound no.	Metris ID no.	Inhibition (%)	IC50 VEGF (μM)	IC50 HUVEC (μM)	Structure
1506-03914	M2025-0006	77	4.5	17	
		70			
		81			
1506-06813	M2025-0007	88	7.3	9.7	
			1.5	8.2	

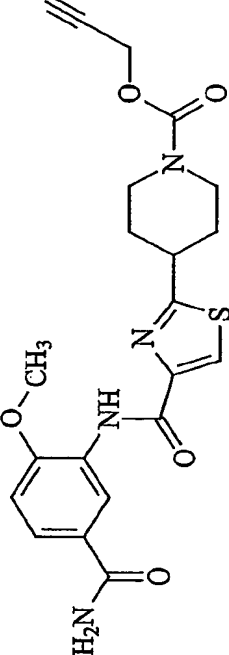
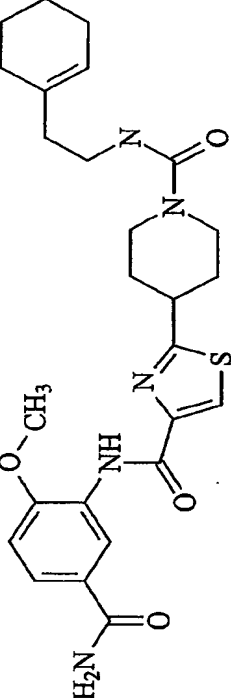
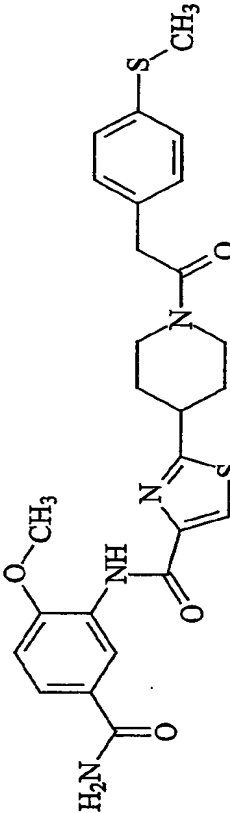
Compound no.	Metris ID no.	Inhibition (%)	IC50 VEGF (μ M)	IC50 HUVEC (μ M)	Structure
1506-08218	M2025-0008	52	14.8	15.4	
		60			
		67			
1506-00404		72	153	10.4	
		-49			
		-35			

Compound no.	Metris ID no.	Inhibition (%)	IC50 VEGF (μM)	IC50 HUVEC (μM)	Structure
1506-00935		65	29		
		51			
		31			
1506-01112		11	16.7	26	
		17			
		55			
1506-01638		89	71	5.4	
		>100	>100	6.0	

Compound no.	Metris ID no.	Inhibition (%)	IC50 VEGF (μM)	IC50 HUVEC (μM)	Structure
1506-01810		-43 -10 -14	136	5.6	
1506-02159		46 -20 -83	128		

Compound no.	Metris ID no.	Inhibition (%)	IC50 VEGF (μM)	IC50 HUVEC (μM)	Structure
1506-03039		63 -13 -67	105	4.2	
1506-03211		64 -24 -80	132		
1506-03388		93 87 90	6.6	23	

Compound no.	Metris ID no.	Inhibition (%)	IC50 VEGF (μM)	IC50 HUVEC (μM)	Structure
1506-03560		42	3.6	16.4	
		88			
		85			
1506-04091		71	16.0		
		56	15.5		
		19			

Compound no.	Metris ID no.	Inhibition (%)	IC ₅₀ VEGF (μM)	IC ₅₀ HUVEC (μM)	Structure
1506-07095		61 -37 -63	173		
1506-07554		84 -15 -83	142	35	
1506-08674		64 84 36	11.0		

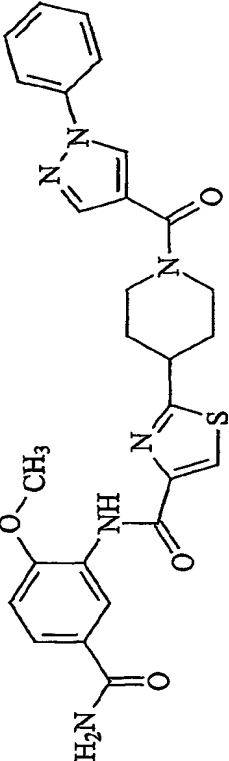
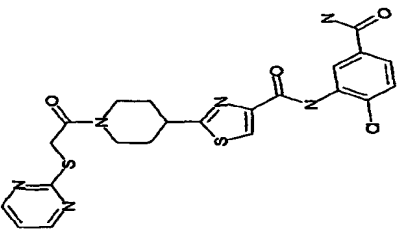
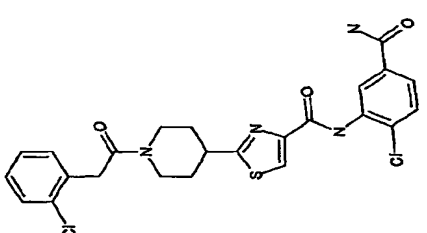
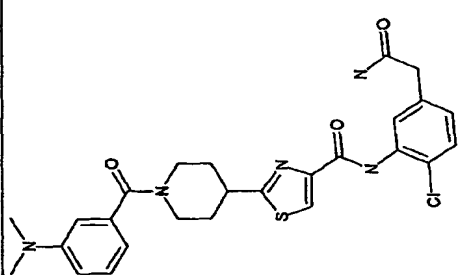
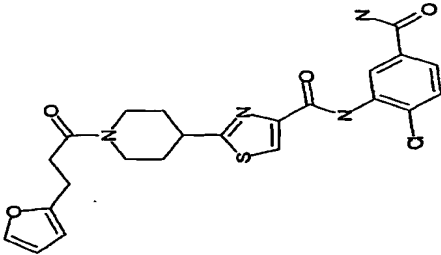
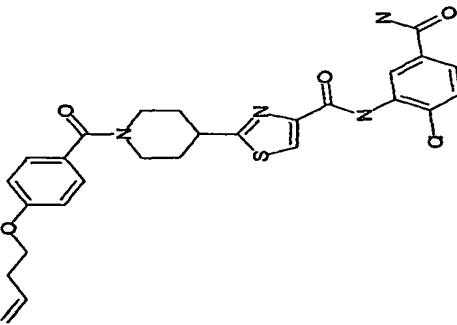
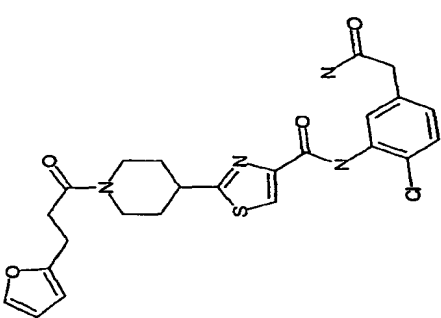
Compound no.	Metris ID no.	Inhibition (%)	IC ₅₀ VEGF (μ M)	IC ₅₀ HUVEC (μ M)	Structure
1506-08772		91	54 126	25	

Table 6
Activities of compounds of the invention

Compound no.	IC50 VEGF (μ M)	IC50 HUVEC (μ M)	Structure
1633-00382	0.655 3.485* 4** 1***	0.938 16* 20** 12***	

1633-00375	5 9**\$			0.448 17**\$
1633-02177	12 18**			0.712 0.478**

1633-00377	5	0.222	
1633-00884	30	0.649	

1633-01861	13	0.803	
------------	----	-------	--

* re-test 3 months later

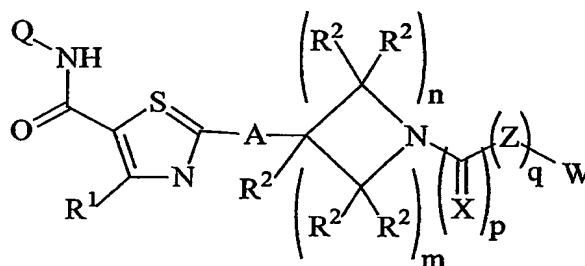
** tested after re-synthesised

*** re-tested in full-concentration response assays

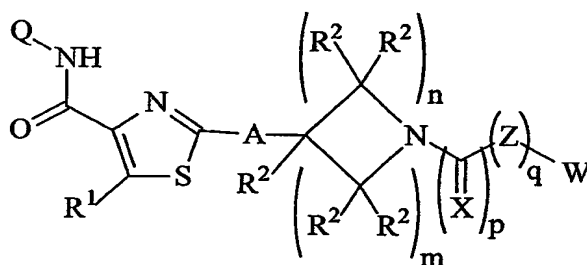
\$ solubility problems

CLAIMS

1. A compound of formula (I) or formula (II):



(I)



(II)

- 10 wherein:

Q is an optionally substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, alkylthio, aralkylthio, amino, alkylamino, dialkylamino, carboxyl, carboxylalkyl, esterified carboxyl, alkylsulfoxyl, alkylsulfonyl, nitro, carbonitrile, carbo-alkoxy, carbo-aryloxy, or heterocyclic group;

- 15 A is a single bond or alkylene;

X is O or S;

Z is O, S or NR^3 ;

p is 0 or 1;

q is 0 or 1;

- 20 n is an integer from 0 to 10;

m is an integer from 0 to 10;

W is an optionally substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, alkylthio, aralkylthio, amino, alkylamino, dialkylamino, carboxyl, carboxylalkyl,

esterified carboxyl, alkylsulfoxyl, alkylsulfonyl, nitro, carbonitrile, carbo-alkoxy, carbo-aryloxy, or heterocyclic group;

R¹ is H or alkyl;

R² is independently H or alkyl; and

5 R³ is H or alkyl;

or a pharmaceutically acceptable derivative thereof.

2. The compound of claim 1 of formula (II).

10 3. The compound of claim 1 or claim 2 wherein A is a single bond.

4. The compound of any of claims 1 to 3 wherein X is O.

5. The compound of any of claims 1 to 3 wherein X is S and Z is NR³.

15

6. The compound of any of claims 1 to 5 wherein R³ is H.

7. The compound of any of claims 1 to 6 wherein p = 1.

20 8. The compound of any of claims 1 to 7 wherein q = 0.

9. The compound of any of claims 1 to 8 wherein the sum n + m is an integer from 2 to 10.

10. The compound of any of claims 1 to 9 wherein the sum n + m is 4.

25

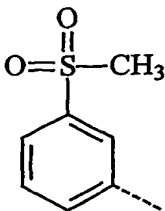
11. The compound of any of claims 1 to 10 wherein n = 2 and m = 2.

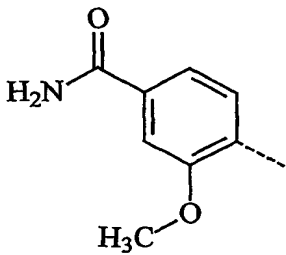
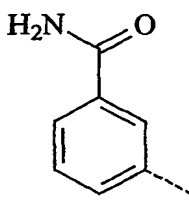
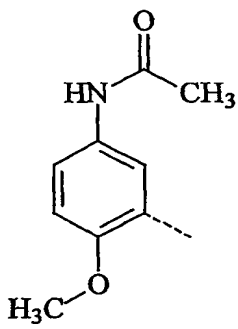
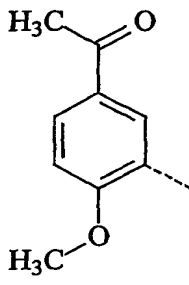
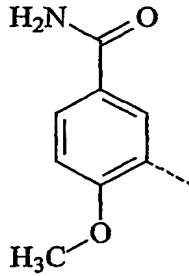
12. The compound of any of claims 1 to 11 wherein R¹ is H.

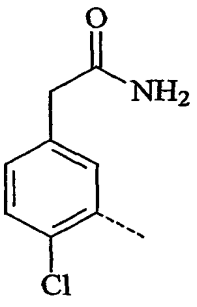
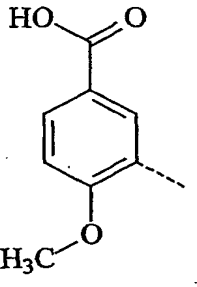
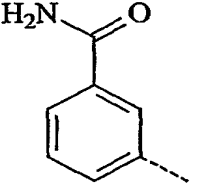
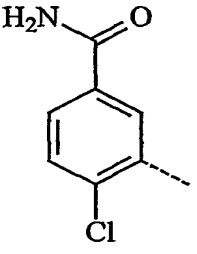
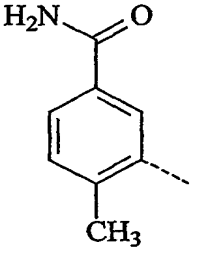
30 13. The compound of any of claims 1 to 12 wherein R² is H.

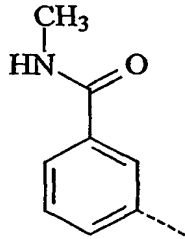
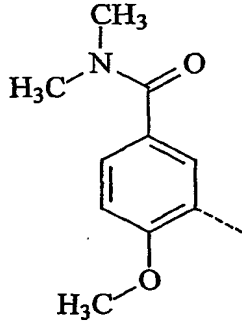
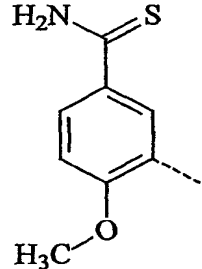
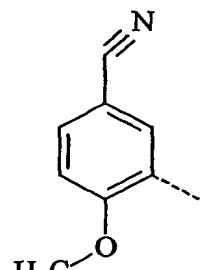
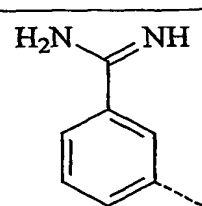
14. The compound of any of claims 1 to 13 wherein Q is an optionally substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, carboxyl, carboxylalkyl, esterified carboxyl, alkylsulfonyl or heterocyclic group.
- 5 15. The compound of any of claims 1 to 14 wherein Q comprises an optionally substituted aryl or heterocyclic group.
16. The compound of any of claims 1 to 15 wherein Q is an optionally substituted aryl or heterocyclic group.
- 10 17. The compound of any of claims 1 to 15 wherein Q comprises an optionally substituted phenyl.
18. The compound of any of claims 1 to 17 wherein Q is an optionally substituted phenyl.
- 15 19. The compound of any of claims 1 to 16 wherein Q is an optionally substituted furanyl.
20. The compound of any of claims 1 to 16 wherein Q is an optionally substituted thienyl.
- 20 21. The compound of any of claims 1 to 16 wherein Q is a radical selected from the radicals set out in table 1.

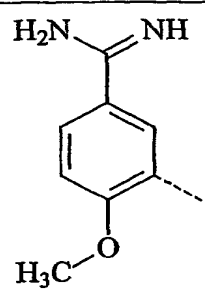
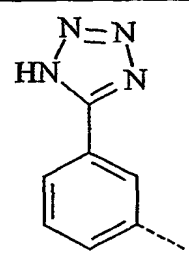
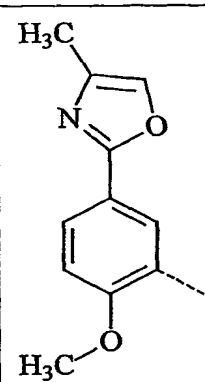
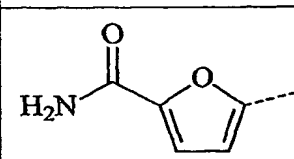
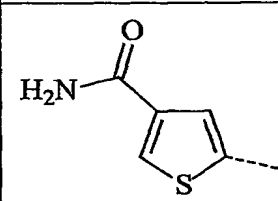
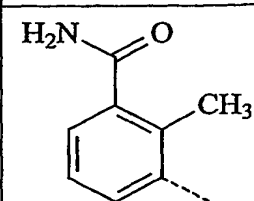
Table 1

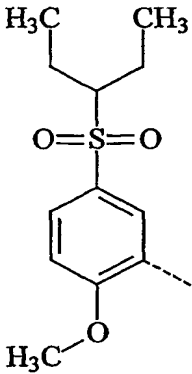
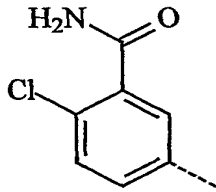
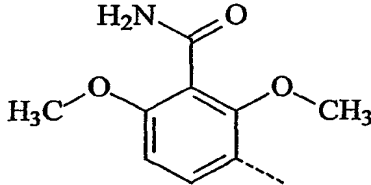
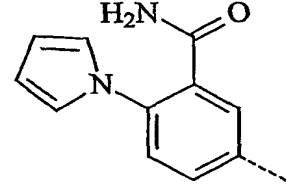
Q	Radical
Q ¹	

Q ²	
Q ³	
Q ⁴	
Q ⁵	
Q ⁶	

Q ⁷	 <p>Chemical structure of a benzene ring with a chlorine atom (Cl) at the 3-position and a carboxamide group (-CH₂-C(=O)-NH₂) at the 4-position. A dashed line indicates a connection point at the 5-position.</p>
Q ⁸	 <p>Chemical structure of a benzene ring with a methoxy group (-OCH₃) at the 3-position and a carboxylic acid group (-C(=O)-OH) at the 4-position. A dashed line indicates a connection point at the 5-position.</p>
Q ⁹	 <p>Chemical structure of a benzene ring with a carboxamide group (-CH₂-C(=O)-NH₂) at the 4-position. A dashed line indicates a connection point at the 3-position.</p>
Q ¹⁰	 <p>Chemical structure of a benzene ring with a chlorine atom (Cl) at the 3-position and a carboxamide group (-CH₂-C(=O)-NH₂) at the 4-position. A dashed line indicates a connection point at the 5-position.</p>
Q ¹¹	 <p>Chemical structure of a benzene ring with a methyl group (-CH₃) at the 3-position and a carboxamide group (-CH₂-C(=O)-NH₂) at the 4-position. A dashed line indicates a connection point at the 5-position.</p>

Q ¹²	 <chem>CN(C(=O)c1ccccc1)c2cc(OC)ccc2</chem>
Q ¹³	 <chem>CN(C(=O)c1cc(OC)ccc1)C(=O)c2ccccc2</chem>
Q ¹⁴	 <chem>CN(C(=O)c1ccccc1)c2cc(OC)ccc2</chem>
Q ¹⁵	 <chem>CN(C(=O)c1ccccc1)c2cc(OC)ccc2</chem>
Q ¹⁶	 <chem>CN(C(=O)c1ccccc1)c2cc(OC)ccc2</chem>

Q ¹⁷	 <p>Chemical structure of 4-amino-3-methoxyphenylhydrazide. It consists of a benzene ring with a hydrazide group (-CONHNH₂) at the 1-position, a methoxy group (-OCH₃) at the 3-position, and a dashed line at the 5-position.</p>
Q ¹⁸	 <p>Chemical structure of 1-phenyl-1H-1,2,4-triazole. It consists of a benzene ring attached to the 1-position of a 1H-1,2,4-triazole ring. A dashed line is shown at the 3-position of the benzene ring.</p>
Q ¹⁹	 <p>Chemical structure of 4-(4-methoxyphenyl)-2-methylisoxazole. It consists of an isoxazole ring with a methyl group at the 2-position, attached to a benzene ring at the 4-position. The benzene ring has a methoxy group (-OCH₃) at the 1-position and a dashed line at the 3-position.</p>
Q ²⁰	 <p>Chemical structure of 2-(4-methoxyphenyl)-5-methylisoxazole-3-carboxamide. It consists of an isoxazole ring with a methyl group at the 5-position, attached to a benzene ring at the 2-position. The benzene ring has a methoxy group (-OCH₃) at the 1-position and a dashed line at the 3-position. A carboxamide group (-CONH₂) is attached to the 3-position of the isoxazole ring.</p>
Q ²¹	 <p>Chemical structure of 2-(4-methoxyphenyl)-5-methylthiazole-3-carboxamide. It consists of a thiazole ring with a methyl group at the 5-position, attached to a benzene ring at the 2-position. The benzene ring has a methoxy group (-OCH₃) at the 1-position and a dashed line at the 3-position. A carboxamide group (-CONH₂) is attached to the 3-position of the thiazole ring.</p>
Q ²²	 <p>Chemical structure of 2-methyl-3-(4-methoxyphenyl)benzamide. It consists of a benzene ring with a carboxamide group (-CONH₂) at the 1-position, a methyl group (-CH₃) at the 2-position, and a dashed line at the 4-position.</p>

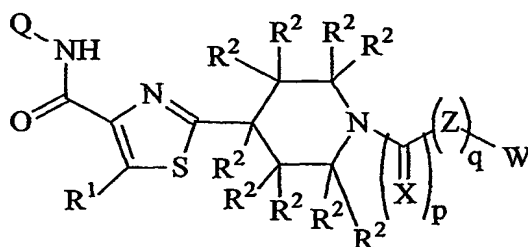
Q ²³	
Q ²⁴	
Q ²⁵	
Q ²⁶	

22. The compound of claim 21 wherein Q is Q₆, Q₇ or Q₁₀.

23. The compound of any of claims 1 to 22 wherein W is an optionally substituted alkyl,
 5 alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, alkylthio, aralkylthio,
 carboxyl, carboxylalkyl, esterified carboxyl, alkylsulfonyl, carbo-alkoxy, carbo-aryloxy or
 heterocyclic group.

24. The compound of any of claims 1 to 23 wherein W is an optionally substituted alkyl,
 10 alkenyl, alkynyl, aryl or heterocyclic group.

25. The compound of any of claims 1 to 24 wherein W comprises an optionally substituted aryl or heterocyclic group.
26. The compound of any of claims 1 to 25 wherein W is an optionally substituted aryl or
5 heterocyclic group.
27. The compound of any of claims 1 to 25 wherein W comprises an optionally substituted phenyl.
- 10 28. The compound of any of claims 1 to 27 wherein W is an optionally substituted phenyl.
29. The compound of any of claims 1 to 25 or 27 wherein W is a benzyl group optionally substituted on the phenyl ring.
- 15 30. A compound of any of claims 1 to 29 having formula (III):



formula (III).

31. A compound of claim 1 selected from:
- 20 *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-{1-[(4,7-dimethylpyrazolo[5,1-*c*][1,2,4]triazin-3-yl)carbonyl]-4-piperidinyl}-1,3-thiazole-4-carboxamide;
- N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-(1-benzofuran-2-ylcarbonyl)-4-piperidinyl]-
25 1,3-thiazole-4-carboxamide;
- N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-(3-phenyl-2-propynoyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide;

2-(1-{[2-(allylsulfanyl)-3-pyridinyl]carbonyl}-4-piperidinyl)-*N*-[5-(aminocarbonyl)-2-methoxyphenyl]-1,3-thiazole-4-carboxamide;

- 5 *N*-[5-(aminocarbonyl)-2-methoxyphenyl]-2-{1-[(2-chlorophenyl)acetyl]-4-piperidinyl}-1,3-thiazole-4-carboxamide;

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-{1-[(3,4-dimethylphenoxy)acetyl]-4-piperidinyl}-1,3-thiazole-4-carboxamide;

10

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-[1-({[4-(dimethylamino)phenyl]amino} carbonothioyl)-4-piperidinyl]-1,3-thiazole-4-carboxamide;

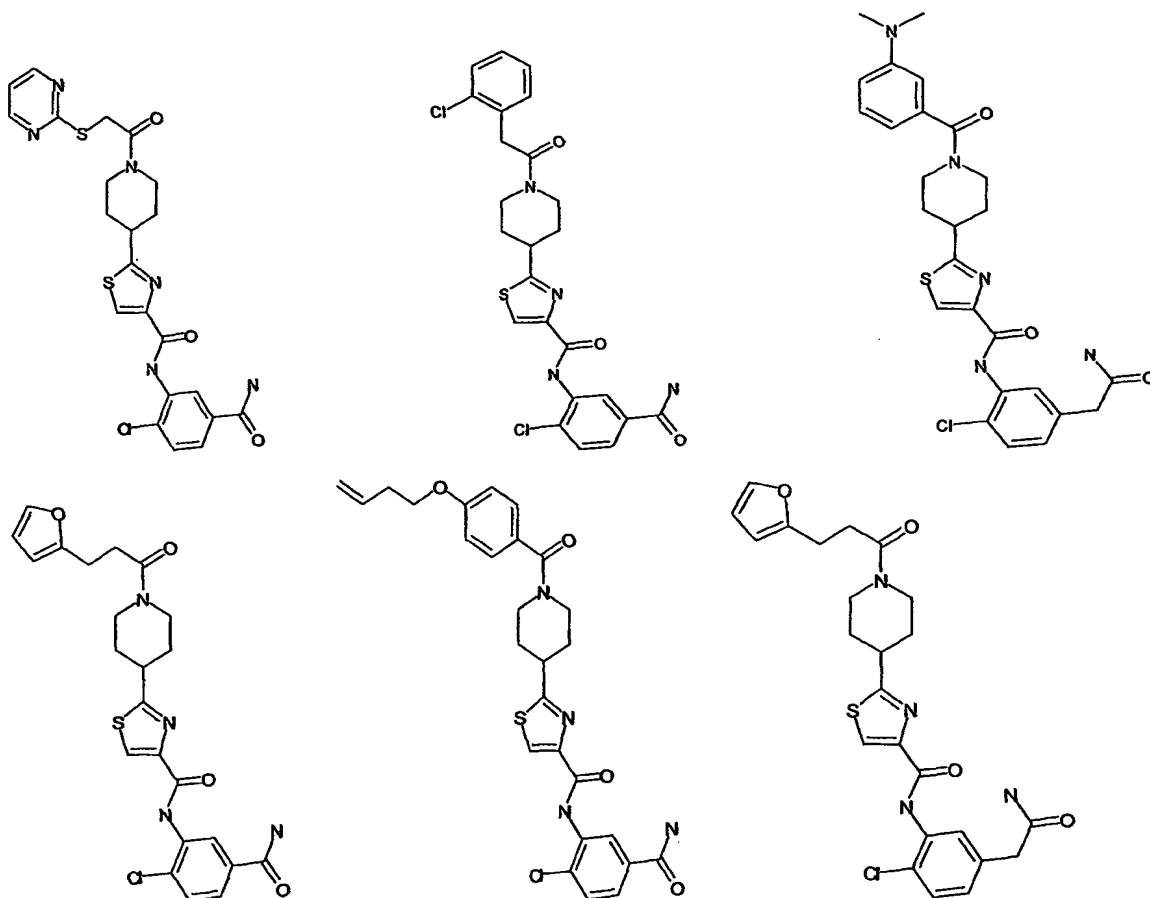
or

15

N-[5-(aminocarbonyl)-2-methoxyphenyl]-2-(1-{[4-(2-pyridinyl)-1-piperazinyl]carbonyl}-4-piperidinyl)-1,3-thiazole-4-carboxamide.

32. A compound of claim 1 selected from:

20



33. The compound of any one of claims 1 to 32 for use in a method of treatment of disease.

5

34. The compound of any one of claims 1 to 32 for use in therapy or diagnosis.

35. Use of a compound of any one of claims 1 to 34 for the manufacture of a medicament for treating a VEGF-mediated disorder.

10

36. The use of claim 35, wherein the condition is endometriosis or cancer.

37. A method of treating a VEGF-mediated disorder comprising administering to a patient in need of such treatment an effective dose of a compound of any one of claims 1-

15 34.

38. A pharmaceutical composition comprising a compound of any one of claims 1-34 in combination with a pharmaceutically acceptable diluent.
39. The use of a VEGF inhibitor for the manufacture of a medicament for treating acute
5 macular degenerative disorder.
40. The use of claim 39 wherein the VEGF inhibitor is a compound of any of claims 1-34.
41. A method of treating acute macular degenerative disorder comprising administering to
10 a patient in need of such treatment an effective dose of a VEGF inhibitor.
42. The method of claim 41 wherein the VEGF inhibitor is a compound of any of claims 1-34.
- 15 43. A VEGF inhibitor for topical administration for the treatment of acute macular degenerative disorder.
44. The VEGF inhibitor of claim 43 which is a compound of any of claims 1-34.
- 20 45. A topical system for the treatment of acute macular degenerative disorder comprising a VEGF inhibitor.
46. The topical system of claim 45 wherein the VEGF inhibitor is a compound of any of claims 1-34.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/GB 03/05651

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D417/04 C07D417/14 C07D487/04 A61K31/427 A61P35/00
/(C07D487/04, 253:00, 231:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 00356 A (GONG YONG ; KLEIN SCOTT I (US); PAULS HEINZ W (US); GUERTIN KEVIN R) 7 January 1999 (1999-01-07) claims; examples 275, 290-293 ---	1, 33-39
A	WO 95 33050 A (SHARKEY ANDREW MARK ; SMITH STEPHEN KEVIN (GB); LYNXVALE LTD (GB);) 7 December 1995 (1995-12-07) claims ---	1, 33, 38
A	US 3 966 748 A (SAFIR SIDNEY ROBERT ET AL) 29 June 1976 (1976-06-29) claims; examples 4, 7, 12, 16, 21 -----	1, 33, 38

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

22 March 2004

Date of mailing of the international search report

01/04/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Chouly, J

INTERNATIONAL SEARCH REPORT

Intern: Application No.
PCT/GB 03/05651

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 37, 41-46 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/05651

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9900356	A	07-01-1999	US 6080767 A	27-06-2000
			AP 1061 A	24-04-2002
			AU 741173 B2	22-11-2001
			AU 8177198 A	19-01-1999
			BG 103264 A	31-01-2000
			BR 9806060 A	31-08-1999
			CA 2264556 A1	07-01-1999
			CN 1236358 T	24-11-1999
			EA 2358 B1	25-04-2002
			EP 0931060 A1	28-07-1999
			HU 0202655 A2	28-11-2002
			JP 2001500532 T	16-01-2001
			NO 990854 A	23-04-1999
			PL 331985 A1	16-08-1999
			SK 22099 A3	09-10-2000
			WO 9900356 A1	07-01-1999
			US 6277865 B1	21-08-2001
			ZA 9805664 A	13-01-1999
WO 9533050	A	07-12-1995	AU 695393 B2	13-08-1998
			AU 2535495 A	21-12-1995
			CA 2191071 A1	07-12-1995
			CN 1159827 A	17-09-1997
			EP 0783571 A1	16-07-1997
			WO 9533050 A1	07-12-1995
			JP 10504183 T	28-04-1998
			NZ 285834 A	28-10-1998
US 3966748	A	29-06-1976	US 6011003 A	04-01-2000
			NONE	